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Clinical trials, consent, and context

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Clinical Trials, Consent, and Context

The Indian Experience

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan

Tilburg University

op gezag van de rector magnificus,

prof.dr. E.H.L. Aarts,

en de University of Edinburgh,

op gezag van de rector,

prof. A. Henderson,

in het openbaar te verdedigen ten overstaan van een
door het college voor promoties aangewezen commissie
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geboren te Haldwani, Nainital, India"

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Abstract

This thesis shows how the perceptions of practitioners and other stakeholders in clinical research in India differ from how informed consent appears in the academic literature and the regulatory framework. My empirical research findings hint at apathy towards the purpose and process of informed consent. I argue that this apathy raises doubts as to the impact of prescriptive work on informed consent in clinical research.

I reach the above conclusion in three broad parts. First, I outline the conceptual framework of informed consent (what makes consent ethically and legally valid) and show how this conceptual framework appears in practice in India and what problems have arisen with regard to the way informed consent is dealt within this contemporary context. Second, I show how informed consent has been legally translated by courts in India and the limits of law in dealing with informed consent in clinical research. Third, I lay out the findings of an empirical research that I conducted in India (between April 2016-October 2016) that reflect stakeholder perspectives on informed consent.

The empirical findings are analysed using the contrasting method where stakeholder perspectives are juxtaposed with how informed consent appears in the academic literature and law. What emerges from my data is a picture that presents a situation where the process of informed consent is oftentimes followed neither as an ethical compulsion nor strictly as a legal obligation. It is not uncommon that researchers consider the process of consent as a mere procedural necessity, thereby performing the action without affording much consideration to either law or ethics. This often leads to apathy towards the ‘larger cause’ (or end goal) of informed consent which, I suggest, is a major reason for the misalignment between ethics, law and the practice of informed consent. To mitigate this misalignment I suggest some non-traditional tools of behaviour regulation alongside the traditional ones.

Declaration

I, Himani Bhakuni, do hereby declare that I have composed this thesis, that the work contained in it is my own, except when otherwise so cited, and that it has not been submitted for any other degree or professional qualification.

Himani Bhakuni
Edinburgh
August 2018

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The learning curve during this PhD phase was steep; I grew not only as a researcher but also as a person and I have Lucas to thank for both. Thank you for making me a better person each day.

List of Abbreviations

AVR	Audio Video Recording
BA/BE	Bio-availability/Bio-equivalence
BMHRC	Bhopal Memorial Hospital and Research Centre
CDRI	Central Drug Research Institute
CDSCO	Central Drugs Standard Control Organisation
CRO	Contract Research Organisation
DCGI	Drug Controller General of India
EC	Ethics Committees
EOW	Economic Offences Wing
GCP	Good Clinical Practice
GCT	Globalised Clinical Trials
IC	Informed Consent
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMR	Indian Council for Medical Research
IEC	Institutional Ethics Committee
INR	Indian Rupee
IRB	Institutional Review Board
MCA	Mental Capacity Act, 2005 (UK)
MHCA	Mental Health Care Act, 2017
MoHFW	Ministry of Health and Family Welfare
NCE	New Chemical Entities
PIL	Public Interest Litigation
PIS	Patient Information Sheet
RCT	Randomised Controlled Trials
SAE	Serious and Adverse Events
SAM	Swasthya Adhikar Manch (case)
SOP	Standard Operating Procedure
TRIPS	Trade Related Aspect of Intellectual Property Rights
WHO	World Health Organisation

GLOSSARY

Academic literature comprises the literature that focuses on defining the conceptual and prescriptive scope of informed consent. It includes work on the ethics of informed consent, what informed consent should look like, and how it should be taken (bearing in mind the capacity and voluntariness of the participant and the adequacy and comprehension of information disclosed to her).

Ethics, for the purposes of this thesis, means broad normative standards that derive from moral principles and are also codified into professional ethical guidelines.¹ These include works of philosophers and practical ethicists on the scope of the concepts that are crucial in describing what informed consent entails.

Legal doctrine (or law) of informed consent means the doctrine as developed through case law and statutes. This excludes pluralistic notions of law.

Process of informed consent means the actions of stakeholders involved in acquiring and giving consent.

Regulatory framework includes the laws, regulations, and ethical guidelines that deal with informed consent in human subject research.

Social facts refer to things such as institutions, norms, values, cultures, etc., which exist external to the individual and affect the behaviour and attitudes of the individual in a given society.

Stakeholders include people who are invested in the process of informed consent within the clinical research spectrum of India.

Web of influences means the external situations or factors that affect a person's behaviour rather than the internal traits of that person.

¹ It is important to clarify that while I am aware of the work of academics who have differentiated between the usage of *ethics* and *morality* within the context of medicine, I look at ethics as stemming from and incorporating morality for most parts of the thesis. This also includes references to ethical guidelines, which derive from ethics, except when I mention ethical guidelines or codes of conduct as part of the regulatory framework. For a further discussion on this and the relationship between medical ethics and law, see I. Brassington, *On the Relationship between Medical Ethics and the Law*, MEDICAL LAW REVIEW, Vol. 26, Issue No. 2, (2018), pp. 225-245.

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INTRODUCTION

This thesis is about differentiating informed consent as it appears in the academic literature and regulatory framework from how stakeholders understand it within the context of clinical research in India. Highlighting such differences is not only important to get a better contextual understanding of the practice of informed consent but also to inform prescriptive work on the matter.

Informed consent appears in three different guises in the academic literature on clinical research: i) as an ethical doctrine, predominantly rooted in the values of autonomy and respect for persons, that aims to promote research subjects' right of self-determination regarding trial participation;¹ ii) as a legal doctrine that prescribes conduct for clinical researchers in their interactions with research subjects and provides penalties for deviations;² and iii) as an interpersonal process through which researchers and subjects interact with each other to chart the course of trial participation and consent to such participation.³ As Berg and colleagues observe, "informed consent is each of these things, yet none of them alone."⁴ Much of the academic literature on informed consent attempts to explain how i) and ii) should be understood to have a practical workable doctrine that best informs iii).⁵ I look at i),

¹ R. R. FADEN & T. L. BEAUCHAMP, *A HISTORY AND THEORY OF INFORMED CONSENT*, (New York: Oxford University Press: 1986).

² J. W. BERG, ET AL., *INFORMED CONSENT: LEGAL THEORY AND CLINICAL PRACTICE*, (2nd edn., Oxford University Press, 2001), p. 3.

³ A. Meisel & M. Kuczewski, *Legal and ethical myths about informed consent*, ARCHIVES OF INTERNAL MEDICINE, Vol. 156, Issue No. 22, (1966), p. 2522; A. Cambon-Thomsen, *The Social and Ethical Issues of Post-Genomic Human Biobanks*, NATURE REVIEWS GENETICS, Vol. 5, (2004), pp. 866-873; L. E. ROZOVSKY, & F. A. ROZOVSKY, *THE CANADIAN LAW OF CONSENT TO TREATMENT*, (Toronto: Butterworths, 1990), pp. 2-3; M. Sheehan, *Can Broad Consent Be Informed Consent?*, PUBLIC HEALTH ETHICS, Vol. 4, (2011), pp. 226-235.

⁴ BERG, ET AL (2001), *supra* note 2.

⁵ Some influential works on the attempt to make informed consent a practical workable doctrine are: BERG, ET AL., (2001), *supra* note 2; J. S. King & B. W. Moulton, *Rethinking Informed Consent: The Case for Shared Medical Decision-Making*, AMERICAN JOURNAL OF LAW & MEDICINE, Vol. 32, (2006), pp. 429-501; J. Katz, *Informed Consent: Must It Remain a Fairy Tale*, JOURNAL OF CONTEMPORARY HEALTH LAW AND POLICY, Vol. 10, (1994), p. 69; N. C. MANSON & O. O'NEILL, *RETHINKING INFORMED CONSENT IN BIOETHICS*, (Cambridge University Press, 1st edn., 2007); S. MACLEAN, *AUTONOMY, CONSENT AND THE LAW*, (Routledge, 2009); P. H. Schuck, *Rethinking Informed Consent*, YALE LAW SCHOOL FACULTY SCHOLARSHIP SERIES, Paper 2765, (1994); R. Heywood, et al, *Informed Consent in Hospital Practice: Health Professional' Perspectives and Legal*

ii), and iii), both individually and together within the Indian context to argue that much of the prescriptive work in the academic literature on informed consent will come to naught if the motivations and perceptions of researchers involved in acquiring informed consent are ignored.

1. Research Problem

The research question that this thesis seeks to address is:

What are the differences between informed consent as outlined in the academic literature and regulatory framework and informed consent as understood by practitioners involved in human subject research in India?

There is consensus in the academic literature on what informed consent entails. Informed consent is legally and ethically valid when competent participants voluntarily join a study after being fully informed of the particulars about the study that could affect their decision to participate in it.⁶ This means that there must be, at the very least, three elements present for consent to research participation to be informed and valid; these are *voluntariness*, *adequate information disclosure*, and *capacity* to consent.⁷ However, these three elements have different latitudes under ethics and law.

It is important to appreciate that while law and ethics are related,⁸ they are both quite distinct fields of study. Both fields provide guidance to humans on how to

Reflections, MEDICAL LAW REVIEW, Vol. 18, Issue No. 2, (2010), pp. 152-184; J. Flory & E. Emanuel, *Interventions to Improve Research Participants' Understanding in Informed Consent for Research: A Systematic Review*, JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, Vol. 292, Issue no. 13, (2004), pp. 1593-1601; and so on.

⁶ FADEN & BEAUCHAMP (1986), *supra* note 1.

⁷ *Id.*; these three essentials are also part of all the ethical guidelines and international instruments pertaining to the conduct of human subject research. *See for example* National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, [Bethesda, Md.]: The Commission, (1978); World Medical Association (WMA), Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects (1964, recently revised in 2013). The said three features are also the legal essentials for consent, *see* Samira Kohli v. Dr. Prabha Manchanda & Anr., (2008) 2 SCC 1.

⁸ As obvious as this claim seems to be, the specific ways in which law and ethics are related are subject to much controversy in legal philosophy. *See* M. S. Moore, *The Various Relations between*

conduct affairs with the larger community. But while ethics discusses what is right and wrong and how we should act to promote the good, law focuses on the minimum acceptable standard or what is institutionally required of each of us.⁹ Law may be informed by ethics, but it has to provide a “single standard of behaviour that provides consistent and coherent guidance”.¹⁰ Conversely, many interpretations of ethical standards can, and do, co-exist.¹¹ The minimum standards laid down by law can only be breached at the risk of civil or criminal liability. However, ethics are geared towards aspirations and goals that we ought to meet, but without (institutionalised) penalties for failing to meet them.¹² Therefore, the legal approach to informed consent is based on a different rationale from that of ethics and creates a different framework within which researchers have to act. The differences between the nature of the two disciplines often leads to the criticism that the legal approach does not have the same vision as that of the ethical approach that strives for the highest moral standard.¹³ This criticism is even stronger when courts translate the principle of informed consent into law as oftentimes essentially ethical considerations are left outside the courtroom.¹⁴

Furthermore, informed consent is often criticised for being a concept that does not match up to its theoretical elucidation in real clinical research settings,¹⁵

Law and Morality in Contemporary Legal Philosophy, *RATIO JURIS*, Vol. 25, Issue No. 4, (2012), pp. 435-471.

⁹ A. R. Maclean, *Magic, Myths, and Fairy Tales: Consent and the Relationship Between Law and Ethics*, In: M. FREEMAN (ED.), *LAW AND BIOETHICS*, (Oxford University Press, 2008).

¹⁰ *Id.* A. R. Maclean (2008).

¹¹ See SATORI report, *International differences in ethical standards and in the interpretation of legal frameworks*, available at <http://satoriproject.eu/media/D3.2-Int-differences-in-ethical-standards.pdf> (last accessed on July 10, 2018)

¹² See further G. Annas, *Ethics Committees: From Ethical Comfort to Ethical Cover*, *HASTINGS CENTER REPORT*, Vol. 21, (1999), pp. 18-21.

¹³ A. J. Weisbard, *Informed Consent: The Law's Uneasy Compromise with Ethical Theory*, *NEBRASKA LAW REVIEW*, Vol. 65, (1986); J. Katz, *Informed Consent - A Fairy Tale? - Law's Vision*, Vol. 39, Issue no. 137, *UNIVERSITY OF PITTSBURGH LAW REVIEW*, (1977).

¹⁴ Some perspectives on why this is the case, see J. Waldron, *Judges as Moral Reasoners*, *INTERNATIONAL JOURNAL OF CONSTITUTIONAL LAW*, Vol. 7, Issue No. 1, (2009), pp. 2-24; C. Foster & J. Miola, *Who's in Charge? The Relationship between Medical Law, Medical Ethics and Medical Morality*, *MEDICAL LAW REVIEW*, Vol. 23, Issue No. 4, (2015), pp. 505-530.

¹⁵ See for example W. A. Silverman, *The myth of informed consent: in daily practice and in clinical trials*, *JOURNAL OF MEDICAL ETHICS*, Vol. 15, (1989), pp. 6-11; P. Alderson, *Informed Consent: Ideal or Reality?*, *JOURNAL OF HEALTH SERVICES RESEARCH & POLICY*, Vol. 3, Issue 2, pp. 124-126; A.

particularly so within the context of developing countries.¹⁶ Therefore, along with outlining the discrepancy between the ethical and legal approaches to informed consent, my research tries to find out how and where the practitioner perspectives differ from these approaches. This is important because only when we figure out where the discrepancies are strikingly evident, and how these affect the realisation of consent in practice, will we be able to think of newer and innovative ways to improve the process.

Informed consent is a multifaceted concept that has been explored using different methods of analysis. The research question outlined here can be answered through different methods of research and analysis. In what follows, I first clarify the scope of this thesis and then justify the use of empirical research to answer the research question.

1.1. Scope of the thesis

The following distinction between two senses of informed consent proposed by Faden and Beauchamp helps delimit the scope of the thesis:

In one sense (...) “informed consent” is analysable as a particular kind of action by individual patients and subjects: *an autonomous authorization*. In the second sense (...) informed consent is analyzable in terms of *the web of cultural and policy rules and requirements of consent that collectively form the social practice of informed consent in institutional contexts* where groups of patients and subjects must be treated in accordance with rules, policies, and standard practices. Here, informed consents are not always autonomous acts, nor are they always in any meaningful respect authorizations.¹⁷ [My emphasis]

This thesis predominantly relies on the *second sense* of informed consent. My goal is to understand the practice of informed consent in the context of clinical research in India. Legal and ethical theories of informed consent are extremely important to this thesis, but the aim here is not to challenge the view that informed consent is an act of

Dawson, *Informed consent: Bioethical ideal and empirical reality*, in: M. HAYRY ET AL., (EDS), *BIOETHICS AND SOCIAL REALITY*, (Amsterdam/New York: Rodopi, 2005), pp. 93-10; G. J. Annas, *Informed Consent: Charade or Choice?*, *THE JOURNAL OF LAW, MEDICINE & ETHICS*, Vol. 45, Issue No. 1, pp. 10-11.

¹⁶ See generally R. MACKLIN, *DOUBLE STANDARDS IN MEDICAL RESEARCH IN DEVELOPING COUNTRIES*, (Cambridge University Press, 2004).

¹⁷ FADEN & BEAUCHAMP (1986), *supra* note 1, pp. 276 - 277.

autonomous authorisation. It is not even to propose a new theory of informed consent. The aim is to show how the principle of informed consent operates within the web of social and policy rules within a given institutional context. This, however, does not imply that I entirely ignore the first sense in my analysis. I do look at autonomy, but only as it appears within the data acquired from my interviewees. The use of autonomy in places before the empirical chapters carries the layperson understanding of it as reflecting a person's capacity to make one's decisions without any controlling influences. In the empirical chapters I use some conceptual formulations of autonomy to supplement stakeholders' perceptions and my research findings. But I remain agnostic on whether protecting participant autonomy is the best justification for informed consent and on the best conceptual definition of it. Therefore, this thesis should not be assessed within the *first sense* of informed consent.

1.1.1. Justification for empirical research

Many enquiries based on ethical principles implicitly rely on empirical propositions. Empirical propositions frame the context of moral judgment and underwrite the justifications of these judgments.¹⁸ Informed consent provides a good illustration of this. Consent, based on the principle of respect for persons, is a fundamental requirement for human subject research.¹⁹ Empirical research has assessed numerous aspects of informed consent for clinical research; this also includes studies on whether subjects have the required understanding of the research study to provide informed consent to participation in the proposed research study.²⁰

¹⁸ F. G. Miller & D. Wendler, *The Relevance of Empirical Research in Bioethics*, SCHIZOPHRENIA BULLETIN, Vol. 32, Issue No. 1, (2006), pp. 37-41.

¹⁹ It has been fundamental aspect of human subject research since it was enshrined in the Nuremberg Code of 1947. See also M. G. del Carmen & S. Joffe, *Informed Consent for Medical Treatment and Research: A Review*, THE ONCOLOGIST, Vol. 10, Issue No. 8, (2005), pp. 636-641; L. O. Gostin, *Informed Consent, Cultural Sensitivity, and Respect for Persons*, JOURNAL OF AMERICAN MEDICAL ASSOCIATION, Vol. 274, Issue No. 10, (1995), pp. 844-845.

²⁰ See for example C. S. Molyneux, et al., *Understanding of informed consent in a low-income setting: three case studies from the Kenyan coast*, SOCIAL SCIENCE & MEDICINE, Vol. 59, Issue No. 12, (2004), pp. 2547-2559; P. Benson, et al., *Information disclosure, subject understanding, and informed consent in psychiatric research*, LAW AND HUMAN BEHAVIOR, Vol. 12, Issue No. 4, (1988), 455-475; M. E. Falagas, et al., *Informed consent: how much and what do patients understand?*, THE AMERICAN JOURNAL OF SURGERY, Vol. 198, Issue No. 3, (2009), pp. 420-435.

Let us assume that an empirical study conducted to assess the comprehension of research participants finds that 57% subjects understand the method of randomisation (that their treatment arm will be selected through a random process and not based on a sound medical judgment for what is best for the participant) in randomised controlled trials (RCTs). The results of the study pose further ethical questions like should we be satisfied that more than half the trial participants understand randomisation or should we be perturbed that almost half the trial participants do not understand the basic study design? Although empirical research *generates* this question, it is not equipped to answer it. The answer depends on what is normatively considered necessary for consent to be valid in RCTs. Yet, because of the results of the first empirical study, some others might consider further empirical research on the methods through which understanding of information could be improved for prospective trial participants of RCTs. Thus, empirical assessments aimed at improving ethical conduct in clinical research are valuable to ethical inquiries. This thesis marks a step in the same direction, albeit the scope of empirical inquiry is different from the ones that I just outlined.

This thesis acknowledges that principles do not exist in a vacuum. They function within a given society where beliefs, practices, perceptions, and attitudes matter. Therefore, my empirical research conducted in India seeks to narrate the perspectives of stakeholders on informed consent. I conducted a multi-stakeholder study that involved interviewing various people concerned with the larger contextual paradigm of consent, this included people who give and take consent (research subjects and researchers), people involved in the regulatory structure of consent, and other invested parties in the process like the civil society, the Clinical Research Organisations (CROs), the public health activists, etc. The interviews with these stakeholders reveal findings pertaining to what they think about informed consent or its various features. Note that not all findings are about how these stakeholders view consent in their given roles. The only stakeholders who talk about consent from their respective roles within the (biomedical research) paradigm are the researchers. Within the interpersonal process of consent, and as the duty-bearers, they are central to understanding the practice of informed consent. The other stakeholders that I interviewed are relevant to informed consent as sponsors of research, regulatory

authorities, and as watchdogs of societal interests, but only come into the frame when there is a problem with the process as performed by the researchers. Therefore, this thesis keeps researcher perspectives central to the empirical claim which is outlined in the next section.

1.2. Grounded proposition of the thesis: central claim

Inspired from the grounded theory methodology, where suppositions are grounded in data collected through systematic research, a grounded thesis was developed through the contrasting method of analysis where the perceptions of stakeholders were contrasted with informed consent as understood in the academic literature and the regulatory framework. The central claim/grounded proposition of this thesis is that scholars and regulators need to acknowledge and understand the perceptions of practitioners and stakeholders involved in acquiring informed consent as failure to address this dimension would render prescriptive work in this area highly questionable.

This claim derives from a methodical process employed to answer the research question outlined in the section above. I answer the primary research question in three broad parts. First, I outline the conceptual framework of informed consent (what makes consent ethically and legally valid) and show how this conceptual framework pans out in India and what problems have arisen with regard to the way in which informed consent is dealt within this contemporary context. Second, I show how informed consent has been legally translated by courts in India and the limits of law in dealing with informed consent in clinical research. Third, I lay out the findings of an empirical research that I conducted in India (between April 2016-October 2016) that reflect stakeholder perspectives on informed consent.

My empirical research findings suggest that the practitioners involved in the process of informed consent regard informed consent as a mere procedural necessity, thereby performing the action without giving much thought to what informed consent is meant to achieve. This disengagement with the purpose of informed consent is evidence of apathy towards the process of informed consent. This apathy, I argue, is possibly a reason why there has been resistance to heavy penalisation for lack of

informed consent in clinical research in India (as will be evident later in the thesis). The indifference to the purpose of consent partially explains why informed consent has largely been reduced to a mechanical process or a tick-box exercise. That is, researchers receive signatures on the consent form but do not engage with the research subjects/participants deeply to make them understand the purpose, risks and benefits, and design of the study. This is usually not a legal problem as there is evidence of consent on paper (unless otherwise challenged) but it is ethically problematic because the understanding and comprehension (of information) threshold is not achieved to make consent ethically valid.

Furthermore, I argue that the apathetic attitude towards the process of consent raises suspicion around the ethics of clinical research in developing countries. Informed consent is often portrayed as the biggest challenge in the ethics of clinical research in developing countries as there is widespread poverty and lack of access to health care.²¹ Though I argue that poverty and lack of access to medical care are not by themselves sufficient to vitiate consent, these harsh situations combined with the high cost of litigation and a lack of a well-defined legal remedy (as will be evident in Chapter 4) means that it is easier for researchers to get away with breaches of informed consent. I say so because the onus to prove a lack of informed consent lies upon the research participant and if the research participant is vulnerable, and does not effectively understand the consequences of trial participation, the chances of exploitation are higher. Therefore, if there is apathy towards the purpose of consent, which means indifference towards participant autonomy and respect for persons, then despite the bare minimum of consent having been reached, the doubt as to whether the research morally *wrongs* participants will always remain.

²¹ This view has been supported by empirical research in developing countries, *see for example* Y. Saidu, et al., *Contextualizing the Informed Consent Process in Vaccine Trials in Developing Countries*, JOURNAL OF CLINICAL RESEARCH & BIOETHICS, Vol. 4, (2013); P. O. Tindana, et al., *Grand Challenges in Global Health: Community Engagement in Research in Developing Countries*, PLOS MEDICINE, Vol. 4, Issue No. 9, (2007); L. Lynoe, et al., *Obtaining Informed Consent in Bangladesh*, THE NEW ENGLAND JOURNAL OF MEDICINE, Vol. 344, (2001); C. S. Molyneux, et al., *'Even if they ask you to stand by a tree all day, you will have to do it (laughter)...!': Community voices on the notion and practice of informed consent for biomedical research in developing countries*, SOCIAL SCIENCE AND MEDICINE, Vol. 61, Issue No. 2, (2005).

My larger empirical research also suggests some reasons for this apathy. Conducting a clinical trial is “time-bound, financially restricted, a regulatory nightmare, and extremely stressful”²² for researchers. My research suggests that most researchers that I interviewed were inclined to prefer the bare minimum (meaning just enough to show that there was no violation of legal rights of the participants) of what would otherwise be an intensive process (meaning a process where researchers are more responsive to the ethical issues and to the informational requirements of the participants). Most prescriptive work on informed consent aims at getting researchers to accommodate the intensive process.²³ The apathy towards the process of informed consent means researchers will likely not be responsive to any sound work on informed consent. They would most likely be unwilling to take into account prescriptive work that aims at improving the existing practice. My small sample size of inquiry cannot predict whether this apathy is widespread, but it shows an inclination towards apathy for the purpose and process of informed consent amongst the interviewed researchers. Such apathy, if widespread, would make it harder to implement newer ways to improve participant comprehension of information, embrace measures to assure participant voluntariness, use multimedia to improve dialogue between researchers-research subjects, and so on. This essentially means that any work on improving the process of informed consent, or how consent should be taken to ensure maximum protection of the trial participant, will come to naught if the practitioners are indifferent to improving the process and are content with the status quo. This is a critical consideration, one that this thesis seeks to address in its contribution to the academic literature, by giving a nuanced analysis of facts and

²² Quoting the terms used by my interviewees for this research, *see* chapters 6 and 7 for further details.

²³ A Google scholar search for “improving informed consent in clinical research” between 1999-2018 returns 17,800 scholarly results. Most cited amongst these include articles favouring the intensive process, *see for example* J. Flory & E. Emanuel (2004), *supra* note 5; P.W. Lavori, et al., *Improving Informed Consent in Clinical Trials: A Duty to Experiment*, CONTROLLED CLINICAL TRIALS, Vol. 20, Issue No. 2, (1999), pp. 187-193; M. Raj, et al., *Improving the Informed Consent Process in Hematopoietic Cell Transplantation: Patient, Caregiver, and Provider Perspectives*, BIOLOGY OF BLOOD AND MARROW TRANSPLANTATION, Vol. 24, Issue No. 1, (2018), pp. 156-162; J. Lentz, et al., *Paving the way to a more effective informed consent process: Recommendations from the Clinical Trials Transformation Initiative*, CONTEMPORARY CLINICAL TRIALS, Vol. 49, (2016), pp. 65-69; P. Agre & B. Rapkin, *Improving Informed Consent: A Comparison of Four Consent Tools*, IRB: ETHICS & HUMAN RESEARCH, Vol. 25, Issue No. 6, (2003), pp. 1-7.

perspectives that may provide a more sustainable ethico-legal basis for future clinical research.

Until now, many scholars have written about the practice of informed consent not matching up to its theory,²⁴ but few have sought empirical evidence to assess the reasons for the existence of such discrepancy. This particularly applies to studies on informed consent in the Indian context. The following section will address why I focus on India for this contextual inquiry into informed consent.

1.3. Why India?

I have taken the example of India to illustrate how the process of informed consent is heavily dependent on *social facts* that the legal and ethical approaches to informed consent often oversee due to their nature. Most academics measure the ethics of clinical trials, and particularly informed consent, against a country's poverty and dismal health care indicators.²⁵ This is why India, a developing country, provides an excellent background to observe the social practice of informed consent within an institutional context. It exemplifies the tensions of a growing economy, with a government that wants to make the global clinical research industry feel welcome in the country, even as a substantive proportion of the population does not have access to basic health care.²⁶ This leaves the government vulnerable to the criticism that it values marketability and economics more than protecting its poor population who

²⁴ See for example E. G. Laforet, *The Fiction of Informed Consent*, JOURNAL OF AMERICAN MEDICAL ASSOCIATION, Vol. 235, Issue No. 15, (1976), pp. 1579-1585; D. Leeb, et al., Observations on the Myth of "Informed Consent", JOURNAL OF AMERICA SOCIETY OF PLASTIC SURGEONS, Vol. 58, Issue No. 3, (1976), pp. 280-282. See also *supra* note 15.

²⁵ J. Schuman, *Beyond Nuremberg, A critique of "Informed Consent" in third world human subject research*, JOURNAL OF LAW AND HEALTH, Vol. 25, (2012), pp. 123-153; L. P. Nijhawan, et al., *Informed Consent: Issues and Challenges*, JOURNAL OF ADVANCED PHARMACEUTICAL TECHNOLOGY AND RESEARCH, Vol. 4, Issue no. 3, (2013), pp. 134-140; R. Fan, *Self-Determination vs. Family-Determination: Two Incommensurable Principles of Autonomy*, BIOETHICS, Vol. 11, Issue No. 3-4, (1997), pp.309-322; A. T. ALORA & J. M. LUMITAO, *BEYOND A WESTERN BIOETHICS: VOICES FROM THE DEVELOPING WORLD*, (Georgetown University Press, 2001), p. 8.

²⁶ Y. Balrajan, et al, *Health care and equity in India*, LANCET, Vol. 377, Issue No. 9764, (2011), pp. 505-515; A. Kapoor, *Why healthcare access eludes India*, THE HINDU, (September 22, 2016), available at <http://www.thehindu.com/opinion/columns/Why-healthcare-access-eludes-India/article14634922.ece> (last accessed on June 2, 2018)

can easily be lured into trial participation.²⁷ A case study of India has been used to make the claim that each clinical research setting is unique and the process of informed consent will differ depending on the setting. Therefore, a homogenous, one-size-fits-all approach to the process of informed consent will not help in achieving its goals.

A perusal of academic literature reveals that numerous justifications have been given for the principle of informed consent. For instance, it protects and promotes the autonomy of the research subject;²⁸ it signifies the right of self-determination over one's body;²⁹ it protects the participant from abusive conduct;³⁰ it acts as a tool for restoration of trust;³¹ it promotes the health and welfare of the research participants,³² and so on. So if the purpose (or goals) of informed consent includes *all* these things, one might be curious as to how (any of) these aims are

²⁷ P. Rawlinson, *Ethics vs. Economics: The Cost of Outsourcing Clinical Trials to Developing Countries*, ELSEVIER SciTECH CONNECT, (June 19, 2015) available at <http://scitechconnect.elsevier.com/clinical-trials-developing-countries/> (last accessed on June 2, 2018); see also G. Porter, *Regulating clinical trials in India: the economics of ethics*, DEVELOPING WORLD BIOETHICS, Vol. 17, (2017). In both these articles, the authors have demonstrated the complex relationship that exists between market forces and the ethics of clinical trials.

²⁸ Informed consent has predominantly been considered an act of "autonomous authorisation" drawing from the works of Faden, Beauchamp, Childress, Dworkin, etc., and since its elaboration as such in The Belmont Report.

²⁹ This idea came from the legal sources, Justice Cardozo's quote "[e]very human being of adult years and sound mind has a right to determine what shall be done with his own body; and a surgeon who performs an operation without his patient's consent commits an assault, for which he is liable in damages" has widely been quoted as the legal justification for informed consent, *Schloendorff v. Society of New York Hospital*, 105 N.E. 92, 93 (1914). See FADEN & BEAUCHAMP (1986), *supra* note 1; T. L. BEAUCHAMP & J. F. CHILDRESS, *PRINCIPLES OF BIOMEDICAL ETHICS*, (Oxford University Press, 2008, 6th edn.); G. DWORKIN, *THE THEORY AND PRACTICE OF AUTONOMY*, (Cambridge University Press, 1988); National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research, (1976), "The Belmont Report", Federal Register, 44(76):23192–23197.

³⁰ For Manson and O'Neill informed consent was necessary to protect people from offences such as bodily assault, coercion, exploitation, and deceit, N. C. MANSON & O. O'NEILL, *RETHINKING INFORMED CONSENT IN BIOETHICS*, (Cambridge University Press, 2007).

³¹ Scholars like O'Neill, Bok, Jackson, etc., informed consent signified a restoration of trust between the patient and the doctor (also the researcher and the research subject). See O. O'NEILL, *AUTONOMY AND TRUST IN BIOETHICS*, (Cambridge University Press, 2002); S. Bok, *Shading the Truth in Seeking Informed Consent for Research Purposes*, KENNEDY INSTITUTE OF ETHICS JOURNAL, Vol. 5, Issue No. 1, (1995), pp. 1–17; J. Jackson, *Telling the truth*, JOURNAL OF MEDICAL ETHICS, Vol. 17, (1991), pp. 5–9.

³² Regarded as the simplest justification of informed consent, N. Eyal, *Informed Consent*, In: E. N. Zalta (Ed.), *THE STANFORD ENCYCLOPAEDIA OF PHILOSOPHY*, (Fall 2012 Edition), available at <https://plato.stanford.edu/archives/fall2012/entries/informed-consent/> (last accessed on June 2, 2018)

realised in a country like India. Such an inquiry is not only timely but also academically relevant. It is timely considering the recent developments in the clinical research spectrum in India. It is also academically relevant because very few, if any, multi-stakeholder studies of the process of informed consent within clinical research have been undertaken in India. My thesis, therefore, adds to the existing literature on informed consent by giving a novel perspective on the process of informed consent in a developing country like India.

1.3.1. The Indian Context

Developing countries, such as India, have become involved in a phenomenon known as the ‘globalisation of clinical trials’ (GCTs). Globalisation (also called off-shoring or outsourcing) of clinical trials refers to the phenomenon where different parts of a drug development process are carried out in different places of the world.³³ In this process, India became one of the preferred destinations for GCTs because conducting a trial in India can potentially reduce the cost of trial by up to 60% due to cheap labour, low infrastructure costs, and easier access to participants.³⁴

To attract international companies, India amended its law to make it more amenable to multinationals. It did so by reforming its patent law in 2005 to align its ‘process patent system’ with the ‘product patent system’ for pharmaceuticals.³⁵

³³ The trend of globalisation in clinical trials led to the revision of the Declaration of Helsinki which contained special provisions for protection of vulnerable population groups in developing countries, see F. P. Crawley, *The 2008 Revised Declaration of Helsinki and Proposed Solutions for Research Ethics in Globalised Clinical Trials*, INTERNATIONAL PHARMACEUTICAL INDUSTRY, (2008), pp. 12-14; For views on globalisation of trials from within the scientific community, see R. Craven, *Testing times for clinical research: Efforts are needed across industry and academia to address scientific and ethical concerns raised by the globalisation of clinical trials*, LANCET, Vol. 9 (2012), pp. 144-145; S. W. Glickman, et al., *Ethical and Scientific Implications of the Globalization of Clinical Research*, THE NEW ENGLAND JOURNAL OF MEDICINE, (2009); For anthropological inquiry into the phenomena of off-shoring of clinical trials see A. PETRYNA, *WHEN EXPERIMENTS TRAVEL: CLINICAL TRIALS AND THE GLOBAL SEARCH FOR HUMAN SUBJECTS*, (Princeton University Press, 2009).

³⁴ For the estimates, see G. Sinha, *Outsourcing drug work: Pharmaceuticals ship R&D and clinical trials to India*, SCIENTIFIC AMERICAN, Vol. 291, (2004), pp. 24–25.

³⁵ See Government of India, Patent Amendment Bill, 2005, See also V. Thawani, K. Gharpure & M. Thawani, *Patent laws must be in the national interest*, INDIAN JOURNAL OF PHARMACOLOGY, Vol. 38, (2006), pp. 70–72. Moreover, the product patent system is recommended by the Agreement on the Trade Related Aspects of Intellectual Property Rights, (TRIPS), which sets down the minimum standards for the regulation by national governments of different forms of intellectual property, and is applicable to the members of the World Trade Organisation (WTO). India initially had a process

When India accepted the product patent system, it granted a higher level of patent protection to the inventor. The amended legislation brought about increased access by innovator companies to the Indian market.³⁶ Along with changes in the patent law, the government allowed drug trials without a ‘phase lag’ in the country, which meant that the government removed the earlier requirement of allowing, for instance, a phase II clinical trial in India only if a phase III trial of the drug had been completed outside India.³⁷ The new rule permitted concurrent trials of the same phase in India that led to an increase in outsourced laboratory work and clinical trials. With increasing policy support from the Indian government, the global pharmaceutical industry became interested in moving its trial operations to India; the move also facilitated easier access to domestic market for the marketing of drugs. All of this made it more appealing for these companies to bring their clinical trials to India.³⁸

patent system, where a patent is granted for a particular manufacturing process, and not for the product itself. This means that the same product can be produced through another process. Such a system led to reverse engineering of a number of products that were already patented elsewhere, thereby establishing a generic pharmaceutical industry in India. In a product patent system, an exclusive right is given to the original inventor of a product. This essentially means that no other manufacturer can provide the same product through the same or any other process. India changed to product patent system in 2005 to become TRIPS compliant. *See generally* K. Chaturvedi & J. Chataway, *Strategic integration of knowledge in Indian pharmaceutical firms: creating competencies for innovation*, INTERNATIONAL JOURNAL OF BUSINESS INNOVATION AND RESEARCH, Vol. 1, Issue No. 1–2, (2006), pp. 27–50; S. K. GUPTA, DRUG DISCOVERY AND CLINICAL RESEARCH, (Jaypee Brothers Medical Publisher, 2011), p. 366.

³⁶ Chaturvedi & Chataway, (2006), *Id.*

³⁷ *Infra* note 39. *See also* D. DEMETS, L. FRIEDMAN & C. FURBERG, FUNDAMENTALS OF CLINICAL TRIALS, (4th edn., Springer, 2010). Pre-clinical trials involve *in vitro* (test tube/cell-culture) and *in vivo* (animal) experiments with the study drug to obtain preliminary information on efficacy, toxicity and pharmacokinetics (how a body reacts to the drugs), to determine if the drug must proceed to Phase I, a preliminary test is done on (about 10) humans in Phase 0 (this test is sometimes skipped to go straight to Phase I). Phase I is to check whether a study drug is ready to check for efficacy – it is tested on 20–100 healthy volunteers for dose ranging. Phase II is the stage where the study drug is not presumed to have any therapeutic effect whatsoever, it is tested on 100–300 patients to assess efficacy and safety of the drug. Phase III trials on 1000–3000 participants are carried out on a large scale in multi-centre environment to assess the effectiveness, efficacy, safety of the study drug and to determine the drug’s therapeutic effect, Phase IV is carried out in effect of post-market and post-registering surveillance of the drug, which is monitoring a drug’s use in public and assessing its long-term effects. Phase III usually involves the clinical researcher and personal physician, whereas Phase IV involves only the personal physician and the participant is anyone seeking any treatment, pertaining to that study drug, from their physician.

³⁸ R. Jeffery, et al., *Big-pharmaceuticalisation: Clinical trials and Contract Research Organisations in India*, SOCIAL SCIENCE & MEDICINE, Vol. 131, (2015), pp. 239–246, p. 240.

In 2005, the government amended Schedule Y of the Drugs and Cosmetics Rules, 1945, appended to the Drugs and Cosmetics Act, 1940. This statute regulates the import, manufacture, distribution, and sale of drugs and cosmetics in India. The amendment of Schedule Y, in 2005, established the guidelines for the conduct of clinical trials in the country.³⁹ Provisions were made in the Schedule to ensure that patients and volunteers participate in studies only after a complete and proper understanding of the investigative study. An elaborate informed consent process, along with the responsibilities of Institutional Ethics Committees (IECs), clinical investigators, and trial sponsors, was outlined in Schedule Y. However, the rapid growth of the clinical research industry soon posed certain problems for the government and the regulatory bodies.

1.3.2. Growth in global clinical trials: opening Pandora's box

Before 2005, one finds only a few documented instances of research conducted without the informed consent of research subjects in India.⁴⁰ However, post 2005, after the sudden growth of the clinical research industry;⁴¹ numerous commentators started alleging regulatory problems in clinical trial regulation in India and casting

³⁹ Schedule Y was introduced in the year 1988 to support the growth of the generic Indian pharmaceutical industry; it contained guidelines related to permissions for clinical trials. It only permitted clinical trials at a phase lower than the global status. The Schedule was later amended (in 2005) to remove the Phase lag, which meant that Phase II-III trials could be carried out concurrently, which facilitated the growth of global clinical development programmes in India. The Schedule was also amended to make it compliant with the ICH-GCP guidelines, thereby introducing guidelines related to informed consent procedures. See A. Bhatt, *Evolution of Clinical Research: A History Before and Beyond James Lind*, PERSPECTIVES IN CLINICAL RESEARCH, Vol. 1, Issue No. 1, (2001), pp. 6-10. See also Amendment, Drugs and Cosmetic Rules of 1945, Schedule Y, vide Subs. G.S.R. 32(E), dated January 20, 2005, available at http://cdsco.nic.in/html/D&C_Rules_Schedule_Y.pdf (last accessed on June 2, 2018)

⁴⁰ A documentation of unethical trials in the world by a non-profit group called SOMO, finds numerous unethical trials from India starting from the 1990s, most of which had inadequate or no informed consent from the trial subjects, for example, the Letrozole Trials, the drug being tested by Sun Pharmaceuticals to induce ovulation. The drug was being tested on about 400 women without their knowledge or consent. See SOMO briefing paper on ethics in clinical trials, *Examples of unethical trials*, (February 2008), available at https://www.wemos.nl/wp-content/uploads/2016/07/examples_of_unethical_trials_feb_2008.pdf (last accessed on June 2, 2018); see also C.M. Gulhati, *Needed: closer scrutiny of clinical trials*, INDIAN JOURNAL OF MEDICAL ETHICS, Vol.12, Issue No. 1, (2004).

⁴¹ V. Bajpai, *Rise of Clinical Trials Industry in India: An Analysis*, INTERNATIONAL SCHOLARLY RESEARCH NOTICES: PUBLIC HEALTH, Vol. 2013 (2013).

doubt over the ethics of some of the trials.⁴² Some even went so far as to call the practice of trials in India by foreign pharmaceuticals and research centres as the “new colonialism”.⁴³ A number of incidents of unethically conducted clinical trials came to be reported in the Indian and the international media between the years 2000-2010.⁴⁴ Despite the media storm, other commentators called the national and international media coverage of “guinea pig” trials in India as “sensationalism”, and pointed out that about 90-95% of trials in India were quality/process compliant.⁴⁵ These commentators asserted that even if a few “outliers” could be identified in the clinical trial spectrum in India, similar ethical lapses could be found in the US or Europe.⁴⁶ Nonetheless, the public outrage culminated in a Public Interest Litigation (PIL).⁴⁷

In the year 2012, prompted by a series of unethically conducted trials reported in the media, the NGO ‘Swasthya Adhikar Manch’ (Health Rights Forum) filed a petition in the Supreme Court of India. The PIL titled *Swasthya Adhikar*

⁴² See for example S. Chattopadhyay, *Guinea pigs in human form: clinical trials in unethical settings*, THE LANCET, Vol. 379, Issue. No. 9830, (2012); G. Vaidyanathan, *Failings exposed at India’s drug regulator*, NATURE, (May 18, 2012); A. Raju, *Indian regulatory system needs to be strengthened to improve clinical trial industry in India: Neuland labs CFO*, PHARMABIZ, (December 23, 2014),

⁴³ S. Nundy & C. M. Gulhati, *A New Colonialism? — Conducting Clinical Trials in India*, THE NEW ENGLAND JOURNAL OF MEDICINE, Vol. 352, (2005), pp. 1633-1636.

⁴⁴ A simple search on the internet would lead to several news stories and documentaries made on unethical trials in India. There are clips ranging from news debates to investigative documentaries recorded on the role of ‘Big Pharma’ in these trials. See for example, A. Buncombe & N. Lakhani, *Without consent: how drugs companies exploit Indian ‘guinea pigs’*, THE INDEPENDENT, (November 14, 2011); S. Lloyd-Roberts, *Have India’s poor become human guinea pigs?*, BBC NEWS, (November 1, 2012); Al Jazeera (Documentary), *Outsourced: Clinical trials overseas*, FAULT LINES AJ, available at <http://www.aljazeera.com/programmes/faultlines/2011/07/2011711112453541600.html> (last accessed on June 2, 2018)

⁴⁵ N. V. Ramamurthy, *Inept media trials of clinical trials*, PERSPECTIVES IN CLINICAL RESEARCH, Vol. 3, Issue No. 2, (2012), pp. 47-49.

⁴⁶ K. Barnes, *Indian clinical trials “of no more ethical risk than in US”*, OUTSOURCING – PHARMA.COM, (September 22, 2006), available at <http://www.outsourcing-pharma.com/Clinical-Development/Indian-clinical-trials-of-no-more-ethical-risk-than-in-US> (last accessed on June 2, 2018)

⁴⁷ In PIL the, *locus standi*, that is the eligibility of a person and the procedures to invoke the jurisdiction of the appellate courts (Supreme Court of India & the High Courts of the States), are so relaxed that anyone asserting a violation of a fundamental right can file a claim in one of the appellate courts. Even letters and telegrams addressed to the Court in violation of a fundamental right have been entertained as PIL’s. However, letters and petitions have to establish a claim of violation of a fundamental right and should not be for pecuniary or other gain (in essence, must not be frivolous litigation). See Supreme Court of India, *Compilation of Guidelines To Be Followed For Entertaining Letters/Petitions Received*, available at <http://supremecourtindia.nic.in/circular/guidelines/pilguidelines.pdf> (last accessed on June 2, 2018)

*Manch v. Union of India*⁴⁸ (hereafter called the SAM case) was brought before the Supreme Court of India asking the Court to intervene in the matter of illegal and unethical trials being conducted on adults, children, and mentally ill people in the country. The interim orders of the Supreme Court in this case have led to an overhaul in the legal and regulatory provisions related to the conduct of clinical trials in the country. In January 2013, after hearing the SAM case, the Supreme Court observed that the “uncontrolled” clinical trials of drugs on human subjects by multinational companies were wreaking “havoc” in the country, noting that the government had slipped into “deep slumber” regarding this “menace.”⁴⁹ The interim orders of the Supreme Court⁵⁰ made the Central Drugs Standard Control Organization (CDSCO), which is the national regulatory body for Indian pharmaceuticals and medical devices, issue a notification making audio-video recording of informed consent proceedings during trials mandatory for all clinical trials.⁵¹ The audio-video requirement for informed consent was later restricted to only ‘vulnerable subjects’,⁵² but the notification did not carry a definition for vulnerable subjects. Moreover, the regulatory bodies decided that to protect the privacy of the participants in anti-HIV or anti-leprosy drug trials only audio (and no video) recording of consent would be required.⁵³

⁴⁸ W. P. (Civil) No. 33 of 2012.

⁴⁹ Report, *SC raps govt slumber on illegal clinical trials*, THE NEW INDIAN EXPRESS (January 4, 2013), available at <http://newindianexpress.com/nation/article1406966.ece> (last accessed on June 2, 2018)

⁵⁰ The status of a pending or disposed of case by the Supreme Court of India, including all interim orders can be found at <http://judis.nic.in/supremecourt/chejudis.asp>

⁵¹ Directorate General of Health Services (DCGI), Order Number: F. No. GCT/20/SC/Clin./2013/DCGI (November, 19, 2013), available at <http://www.cdscsco.nic.in/writereaddata/Office%20Order%20dated%2019.11.2013.pdf> (last accessed on June 2, 2018)

⁵² This was done because concerns were raised about the logistics of the audio-video recording procedure. It also raised some privacy concerns. Moreover, a study among a rural community studying the willingness of participants to be recorded during the consent process found that more than one-third of the participants refused to be video-taped, see R. C. Chauhan, et al, *Consent for audio-video recording of informed consent process in rural South India*, PERSPECTIVES IN CLINICAL RESEARCH, Vol. 6, (2015), pp. 159-162; S. Nadimpally & D. Bhagianadh, “The invisible”: *Participant's experiences in clinical trials*, PERSPECTIVES IN CLINICAL RESEARCH, Vol. 8, (2017), pp. 5-10.

⁵³ Ministry of Health and Family Welfare, Gazette Notification G.S.R. 611/(E), (July 31, 2015), available at <http://www.ferci.org/wp-content/uploads/2014/07/Gazette-Notification-31-July-2015-AV-consent.pdf> (last accessed on June 2, 2018)

In the aftermath of the SAM case, clinical research in India is still governed under the Drugs and Cosmetics Act, 1940. However, an amended Schedule Y has introduced the requirement to make an audio-video recording (hereafter AVR) of informed consent mandatory for vulnerable subjects. Some guidelines were released by the CDSCO on how AVR is to be done in order to comply with rules regarding privacy and confidentiality of the research subjects.⁵⁴ However, there is ambiguity surrounding the vetting of the consent tapes and the definition of vulnerable subjects. No strict penalties have been introduced for the violation of ethical guidelines during the conduct of research, not even for the violation of informed consent. Post the SAM case, new regulations pertaining to the conduct of trials were released, which led to a brief lull and a negative impact on the growth of the clinical research industry.⁵⁵ But as of 2017, commentators suggest that the period of regulatory uncertainty is over and the environment is once again conducive for the conduct of clinical research. Nonetheless, some commentators are cautious about this optimism as they warn against the overselling of the “hyped potential”⁵⁶ of the Indian market. Some advise that the future of trials should be about “human protection” and not just about attracting more research sponsors to India.⁵⁷

1.3. The Inquiry in Context

Given this background, one could make a long list of issues that merit scholarly inquiry. However, inadequate informed consent procedures were at the heart of the

⁵⁴ Central Drugs Standard Control Organisation, Draft Guidelines on Audio-Visual Recording of Informed Consent Process in Clinical Trials, Guidance Document, (January 9, 2014), available at http://www.cdsc0.nic.in/writereaddata/Guidance_for_AV%20Recording_09.January.14.pdf (last accessed on June 2, 2018)

⁵⁵ A. Nair, *Clinical research: Regulatory uncertainty hits drug trials in India*, PHARMACEUTICAL JOURNAL, (March 12, 2015); for an overview of what the current regulatory scene is and what could be expected in the future, see A. Bhavé & S. Menon, *Regulatory environment for clinical research: Recent past and expected future*, PERSPECTIVES IN CLINICAL RESEARCH, Vol. 8, Issue No. 1, (2017), pp. 11-16.

⁵⁶ Thereby implying that India being a clinical research friendly destination with a huge potential for growth was just a story sold to attract foreign investment into the clinical research industry, see Nair, (2015), *Id.*

⁵⁷ A. Bhatt, *Future of Indian clinical trials: Moving forward from hyped potential to human protection*, PERSPECTIVES IN CLINICAL RESEARCH, Vol. 8, Issue No. 1, (2017), pp. 2-4; See also A. Venkatesh, ‘Now, India has a balanced, scientific regulatory framework for clinical trials’, BIOSPECTRUM ASIA, (June 6, 2017).

series of unethical trials that led to the SAM case. Although this case prompted major changes in the clinical research regulation in India, it had some flawed premises and generalisations. The petitioners in the SAM case made no distinctions and termed all foreign sponsored trials conducted in India as “guinea-pig” trials that have no respect for participant rights.⁵⁸ This led to notoriety for the clinical research industry. The media reports also lacked a nuanced approach to debate. All this led to the condemnation of GCTs, a subject that has been discussed in numerous books, papers, and articles as a phenomenon that is inherently exploitative.⁵⁹ However, one article stands out for its careful consideration in addressing the globalisation of biomedical trials. Lang and Siribaddana lay out multiple reasons why such globalisation is necessary.⁶⁰ They note that there is an under-representation of populations of developing countries in clinical research. They also note that research sites in developing countries benefit extensively from externally sponsored trials in terms of capacity development and much-needed investment. They stress the need for newer and different approaches to tackling diseases and health issues particularly in low-income settings.

Lang and Siribaddana take due note of the possibility of exploitation of vulnerable population groups in developing countries. Even so, they think that such a possibility for exploitation can be reduced if the trials in developing countries contribute to the development of clinical trial research methodology by having trial operations that are specific to the risk and complexity of each trial.⁶¹ Such nuance is lacking in much of the literature on informed consent in developing countries, as conditions of poverty, illiteracy, and poor health care are usually the starting point

⁵⁸ *Supra* note 48.

⁵⁹ K. S. Rajan, *Experimental Values*, NEW LEFT REVIEW, Vol. 45, (May-June, 2007); P. Lurie & S. M. Wolfe, *The Ethics of Clinical Research in the Third World*, THE NEW ENGLAND JOURNAL OF MEDICINE, Vol. 337, Issue No. 12, (September, 1997), pp. 847-849; R. MACKLIN, *DOUBLE STANDARDS IN MEDICAL RESEARCH IN DEVELOPING COUNTRIES*, (Cambridge University Press, 2004); S. R. Benatar, *Imperialism, research ethics and global health*, JOURNAL OF MEDICAL ETHICS, Vol. 24, (1998), pp. 221-222.

⁶⁰ T. Lang & S. Siribaddana, *Clinical trials have gone global – is this a good thing?*, PLOS MEDICINE, Vol. 9, Issue No. 6, (2012).

⁶¹ But to do this research sponsors and CROs need to rethink their one-size-fits-all approach to clinical trial operations. This also means that the informed consent process should not be ‘standardised’ as it usually is for a corporate or CRO sponsored trial, Lang & Siribaddana, *Id.*

for discussion. In order to adopt a nuanced approach and to find newer ways to improve the process of informed consent, it is important to understand the perspectives of different stakeholders involved in the process.

One must bear in mind that in between the interim Supreme Court orders on the SAM case and the new regulations released by the CDSCO, there was a period of uncertainty in the regulatory infrastructure related to clinical trials. This period lasted about two years and led to a significant decrease in clinical trials in India.⁶² This was detrimental to the growth of the clinical research capacity of the country. To put this into perspective, India spends less than 3% of its GDP on health (it rose from 1.1. to 2.5% in the 2017 annual budget).⁶³ This leaves very little for spending on health and clinical research. Investment by foreign sponsors could provide the necessary funds to sustain and promote biomedical research in the country. Certainly, such promotion should not come at the cost of lives and health of Indian citizens. This is why biomedical research ethics and stringent regulations are important. But despite the fact that the Supreme Court issued *bona fide* interim orders based on the, somewhat broad, claims made by petitioners in the SAM case, it is important that we at least attempt to determine the precision of those claims. This is why the views of the practitioners are central to this thesis.

Furthermore, examples of unethical trials from India, which I will discuss in the next chapter, reveal that while there have been problems with the informed consent procedures, these have not usually given rise to formal legal action. Nevertheless, informed consent is often regarded as not merely an ethical necessity but also a legal one. Although informed consent is not the only requirement to make clinical research ethical, it has a status akin to a non-derogable right in international

⁶² Press Trust of India, *Post stringent norms, clinical trials in India plummet*, THE HINDU, (April 21, 2013), available at <http://www.thehindu.com/sci-tech/health/policy-and-issues/post-stringent-norms-clinical-trials-in-india-plummet/article4639976.ece> (last accessed on June 2, 2018)

⁶³ Special Correspondent, *Health spending to be 2.5% of GDP*, THE HINDU, (March 17, 2017), available at <http://www.thehindu.com/news/national/centre-cleared-the-long-awaited-national-health-policy-2017/article17487845.ece> (last accessed on June 2, 2018)

law.⁶⁴ Yet, despite the large academic literature surrounding informed consent, it remains an enigma, the practice of which rarely lives up to its theory.

Albeit there are rules pertaining to informed consent in the form of statutory and ethical guidelines, the biggest question that remains unanswered is why these rules are sometimes disregarded or unenforced. Is the problem as simple as lax enforcement of rules or are there deeper issues underlying the attitude towards informed consent? As noted above, after conducting my fieldwork and having completed my literature review, I come to the conclusion that informed consent is mostly viewed as a procedural necessity and practitioners barely think about what the process purports to achieve. The question of informed consent then is not just about the ethics or law; it is about the individual's motivation to fulfil its requirements. However, in reaching this conclusion I went through a systematic research process. The following section will outline the structure and the research process that went into addressing the research question as outlined in Section 1.

1.4. Structure of the thesis

Chapter 2 contextualises the thesis within the larger debates on globalisation of clinical research. The chapter is supplemental to the central argument of this thesis, but it does the important job of placing the content of this thesis within a global context.

Chapter 3 is divided into two parts. Part 1 defines the idea of informed consent (IC) in research. It gives a brief history of IC, and outlines the differences between the research and the treatment context. It goes on to give a brief conceptual framework of IC (i.e., the three essentials as legally and ethically understood by outlining the theoretical consensus on what voluntariness, information, and capacity entails). Part 2 describes how this conceptual framework is transplanted into the larger contextual setting of India. It looks at what IC looks like within the Indian context and what

⁶⁴ A non-derogable norm of international law means a rule so fundamental to the international legal order that it cannot be set aside or suspended, even upon the express consent of states, for instance, right to life. Similarly, informed consent cannot be set aside. However, unlike a non-derogable norm there are some exceptions to this, like emergency cases for treatment and studies with minimal risk in research.

problems regarding informed consent have arisen in the past. It uses some examples of unethical trials cited in the SAM case to discuss how these examples reflect the differences between informed consent in academic literature and the clinical research practice in India. This chapter ends on the note that the elucidation of consent operating within the Indian context will not be complete till we take account of law's role in regulating informed consent as well as the limitations of law in regulating this field.

Chapter 4 is divided into three parts. Part 1 talks about the law of informed consent in India. The focus is on the treatment context since the legal doctrine on informed consent has been shaped around it. It looks at how India borrows IC law from other common law jurisdictions and employs socio-economic reasoning to choose between standards. It shows how the legal standards set in the treatment context would not be conducive to clinical research settings. Part 2 looks at the IC law within the research context. In the absence of an established legal doctrine specific to the research context, it looks at the possible legal avenues under which a claim for lack of IC in research can be entertained. It also looks at how the law in other common law countries has developed around IC in clinical research, and how similar cases could be dealt with by the Indian courts. Part 3 highlights the limits of the law in dealing with IC as a process. It talks about legalism as a potential problem which elevates the legal standards to the level of ethical standards, thereby adding to the apathy towards the purpose of informed consent. The chapter ends by highlighting the need for empirical data to look at how IC translates to real clinical research practice and to inquire if legalism is prevalent in the Indian clinical research spectrum. It places emphasis on the fact that the legal and ethical frameworks give a partial understanding of informed consent within any given context. The perceptions of stakeholders involved in the process are crucial not only to gathering a more comprehensive contextual understanding but also to formulate any prescriptive methods to better the IC procedures.

Chapter 5 describes the research methodology chosen for the empirical component of the thesis. It leads the reader through the step-by-step process of collecting,

organising, coding, and analysing the perspectives of various stakeholders involved with clinical research in India.

Chapters 6 and 7 enumerate the research findings under five themes; these include the three essentials of informed consent - voluntariness, information disclosure, and capacity (in chapter 6) - and supplementary themes on the justifications for informed consent and the role of law and ethics (in chapter 7). The analysis is presented alongside the research findings with theoretical, doctrinal, and empirical works on informed consent pitched against the views of the stakeholders.

Chapter 8 contains a reflective analysis and creates a grounded proposition based on the research findings which suggest that, amongst the stakeholders involved in acquiring consent in India, there is a degree of apathy towards the process of informed consent. In response to this, I suggest the use of incentives and nudging in addition to the more traditional forms of regulating human conduct like clearer laws, stronger enforcement, rigorous ethics training, and better oversight of IC procedures.

CONTEXTUALISING THE THESIS

2.0. Introduction

This chapter places the thesis within the larger context of clinical research in developing countries. This chapter, although important to grasp the bigger picture, is supplementary to the central argument of the thesis which focuses on a much narrower research question, that is, on the interactions between the principle, doctrine, and practice of informed consent within the Indian clinical research context. Nevertheless, a more general contextualisation is warranted to understand the place of this thesis within the larger debates on globalisation of clinical research.

The chapter begins by detailing the problems that arose when global pharmaceutical corporations started moving their clinical trials from the global north to the global south. It then elaborates upon the global responses to these problems in the form of additions made to the existing international normative instruments on human subject research. The chapter ends by reiterating the scope of the thesis and positioning it within a global context.

2.1. Clinical Research in the Global South

Globalization of clinical research has arisen for many reasons, but chiefly due to the need for quicker and economically efficient studies.¹ Globalisation has enabled the conduct of multinational studies with sponsors, investigators, and participants spread across different locations around the world. A 2014 study analysing the geographic distribution of multinational trials found that globalisation of trials started its slow and steady rise around the 1980s.² Although Europe with a 58.1% share in multinational trials and North America with 18.5% were revealed to be the dominant players in terms of participation in such trials, the study showed a marked increase in trials conducted in the non-traditional markets of Latin America (from 2.5 in the

¹ T. Lang & S. Siribaddana, *Clinical Trials Have Gone Global: Is This a Good Thing?*, PLOS MEDICINE, Vol. 9, Issue No. 6, (2012); J. Hoekman, et al., *The Geographical Distribution of Leadership in Globalized Clinical Trials*, PLOS ONE, Vol. 7, (2012).

² T. A. Richter, *Clinical Research: A Globalized Network*, PLOS ONE, Vol. 9, Issue No. 12, (2014).

1990s to 5.3% in 2014) and Asia (from 4.3% to 12.1%).³

The increase in multisite trials in non-traditional markets, particularly in developing countries, has led to numerous instances that have called the ethics of such trials into question.⁴ For instance, during the *Nevirapine* (anti-transmission HIV drug) clinical trials conducted in Uganda between 1997 and 2003, and sponsored by Boehringer Ingelheim, the investigators allegedly failed to obtain the consent of participants regarding changes in the design of the study and also administered incorrect doses of the drug.⁵ In Hyderabad, India during the 2003 trials of the anti-clotting drug *Streptokinase*, it was alleged that the subjects were uninformed of their participation in the trial and the mandatory regulatory permissions were not taken by the multinational sponsors.⁶ The 1996 *Trovaflaxin* (Trovan for meningococcal meningitis) trials by Pfizer in Nigeria, during the course of which 11 children died and many others were left disabled,⁷ also garnered much scholarly and media attention.⁸ The survivors of the Trovan trials brought four law suits against Pfizer in the US alleging that the trials were done without ethical approval, without informed consent of the guardians of the children, and without due standard of care.⁹ Three of these lawsuits were dismissed on procedural grounds¹⁰ and Pfizer eventually settled the rest out-of-court.¹¹ The DART trials conducted in Uganda, Ivory Coast, and

³ In 2014 Oceania's share in multinational trial participation was 3.7% and Africa had a 2.6% share. *Id.*, Richter (2014).

⁴ For a detailed analysis of 21 trials from different developing countries, see J. V. LAVERY, ET AL., (EDS.), *ETHICAL ISSUES IN BIOMEDICAL RESEARCH: A CASEBOOK*, (Oxford University Press, 2007).

⁵ SOMO briefing paper on ethics in clinical trials, Examples of unethical trials, (February 2008), available at

https://www.wemos.nl/wpcontent/uploads/2016/07/examples_of_unethical_trials_feb_2008.pdf

⁶ It was also alleged that there was some link between the drug administered and the eight deaths that occurred during the course of the trials. *Id.*, SOMO paper (2008).

⁷ J. Wise, *Pfizer accused of testing new drug without ethical approval*, *BRITISH MEDICAL JOURNAL*, Vol. 327, (2001), p. 194.

⁸ See for example T. Ready, *Pfizer in "unethical trial" suit*, *NATURE MEDICINE*, Vol. 7, (2001), p. 1077; J. Stephens, *Panel Faults Pfizer in '96 Clinical Trial In Nigeria*, *WASHINGTON POST*, (May 7, 2006), available at

<http://www.washingtonpost.com/wp-dyn/content/article/2006/05/06/AR2006050601338.html> (last accessed August 15, 2018); J. Lenzer, *Secret report surfaces showing that Pfizer was at fault in Nigerian drug tests*, *BRITISH MEDICAL JOURNAL*, Vol. 332, (2006).

⁹ *Abdullahi v. Pfizer, Inc.*, 2002 U.S. Dist. LEXIS 17436 (S.D.N.Y. September 17, 2002); *Abdullahi v. Pfizer, Inc.*, 77 Fed. Appx. 48, 2003 U.S. App. LEXIS 20704 (2d Cir. N.Y., October 8, 2003); *Abdullahi v. Pfizer, Inc.*, 2005 U.S. Dist. LEXIS 16126, (S.D.N.Y., August 9, 2003).

¹⁰ *Id.*

¹¹ See S. Boseley, *WikiLeaks cables: Pfizer 'used dirty tricks to avoid clinical trial payout*, *THE GUARDIAN*, (December 9, 2010), available at

Zimbabwe in 2003 were meant to compare the different methods to administer the anti-retroviral therapy for the treatment of HIV. These trials highlighted the unethical conduct of the researchers when it was found that the patients on the less successful treatment arm were not switched back to the successful one despite a regulatory body associating the former with a higher risk of disease.¹²

But perhaps the most prominent trials that started the international discourse on the ethics of clinical research in developing countries were the AZT trials. A number of controversies came to be associated with the placebo-controlled AZT trials conducted in the 1990s across 15 sites including Thailand, Dominican Republic, and 9 countries in sub-Saharan Africa.¹³ Due permissions and approvals were taken in each of the trial sites before the commencement of the trials. Trials for a short-duration regimen of the AZT drug were conducted on pregnant women who were seropositive for HIV and were randomized so that the women received either AZT or a placebo in the final weeks of pregnancy and during labour. It must be noted that the AZT drug with a successfully trialled and proven 076 regimen was already considered the *de facto* standard of care in most developed countries. These placebo-controlled trials were conducted to assess a modified regimen of 076 which would be of shorter duration, simpler, similarly effective, more cost-effective, and therefore, affordable in developing countries.

Being a placebo-controlled trial, neither the pregnant woman nor any clinician was aware of what each woman was receiving. The woman's new-born was tested several times for HIV over a period of 18 months. New mothers in some of the trials were instructed not to breastfeed prior to testing the new-borns since breast milk can also transmit the virus. This was done to reduce cases of HIV transmission that had the possibility to render the trials inconclusive. The participants received free medical care for the entire period of the study. But after the completion of the

<http://www.theguardian.com/business/2010/dec/09/wikileaks-cables-pfizer-nigeria> (last accessed on July 8, 2018); See also Ford & Tomossey, *Clinical Trials in Developing Countries: The Plaintiff's Challenge*, LAW SOCIAL JUSTICE AND GLOBAL DEVELOPMENT JOURNAL, Issue No. 1, 2004 (Electronic Law Journal), available at http://www2.warwick.ac.uk/fac/soc/law/elj/lgd/2004_1/ford/ (last accessed on July 2, 2018)

¹² SOMO briefing paper (2008), *supra* note 5.

¹³ C. L. Wendland, *Research, Therapy, and Bioethical Hegemony: The Controversy over Perinatal AZT Trials in Africa*, AFRICAN STUDIES REVIEW, Vol. 51, Issue No. 3, (2008), pp. 1-23.

study the participants and their new-borns were not offered any additional antiretroviral medications.¹⁴

The AZT trials faced enormous scholarly backlash.¹⁵ Some critics questioned the procedure for recruiting trial participants at the research sites.¹⁶ They argued that widespread poverty, illiteracy, and poor access to health care in most of the research sites meant that for most participants the only way to get any medical care was to enrol in the trial.¹⁷ Others raised the issue of the ultimate beneficiaries of these trials, as the high cost of the approved drug was likely to preclude the population of these countries from accessing the benefits of the drug.¹⁸ Some considered the design of placebo-controlled trials as contrary to international human rights instruments that require every patient to receive the best available medical care.¹⁹ A different critique invoked the international guidelines on placebo-controlled trials and argued that placebo trials were discouraged where effective therapies existed, and because proven therapies existed there was no need to conduct the AZT trials.²⁰ The supporters of the AZT trials, however, asserted that no existing therapies were sold or marketed in the research sites at the time of the trials and thus no alternate therapies existed.²¹

¹⁴ *Id.*

¹⁵ Lurie, P. & Wolfe, S. M., *The Ethics of Clinical Research in the Third World*, THE NEW ENGLAND JOURNAL OF MEDICINE, Vol. 337, Issue No. 12, (September, 1997). This article not only started the discussions and debates around the AZT trials but is also often credited as the starting point of discussions on the ethics of clinical research in developing countries, see Wendland (2008), *supra* note 13.

¹⁶ E. Tafesse & T. Murphy, *Ethics of Placebo-Controlled Trials of Zidovudine to Prevent the Perinatal Transmission of HIV in the Third World*, THE NEW ENGLAND JOURNAL OF MEDICINE, Vol. 338, (1998); H. French, *AIDS Research in Africa: Juggling Risks and Hopes*, NEW YORK TIMES, (October 9, 1997), available at <https://www.nytimes.com/1997/10/09/world/aids-research-in-africa-juggling-risks-and-hopes.html> (last accessed on July 30, 2018)

¹⁷ *Id.*

¹⁸ Annas, G. J. & Grodin, M. A., *Human Rights and Maternal-Fetal HIV Transmission Prevention Trials in Africa*, AMERICAN JOURNAL OF PUBLIC HEALTH, Vol. 88, (1998).

¹⁹ R. Bayer, *The Debate over Maternal-Fetal HIV Transmission Prevention Trials in Africa, Asia and the Caribbean: Racist Exploitation or Exploitation of Racism?*, AMERICAN JOURNAL OF PUBLIC HEALTH, Vol. 88, Issue No. 4, (1998).

²⁰ *Id.*

²¹ R. Levine, *The 'Best Proven Therapeutic Method' Standard in Clinical Trials in Technologically Developing Countries*, 1RB: A REVIEW OF HUMAN SUBJECTS RESEARCH, Vol. 20, Issue no. 1, (1998).

The articles critiquing the AZT trials made international headlines²² and as more people began writing about the controversy, comparisons began being drawn between the AZT trials and the notorious Nuremberg and Tuskegee trials.²³ With such dire comparisons, the Gambian government (one of the 9 sub-Saharan research sites) responded by asserting that:

Research ethics committees in developing countries can learn from debates elsewhere. However, if commentators from affluent societies dismiss the decisions of these local committees as unethical the developing world will make the justifiable charge of ethical imperialism. Ethics cannot be owned by affluent countries alone. Ethics committees such as The Gambia's are just as capable of acknowledging and operating under proper standards of research ethics.²⁴

On the heels of the controversies surrounding the AZT trials, bioethicists and researchers involved in the working groups and committees of the organisations governing research updated the international research ethics guidelines and other international normative instruments guiding human subject research. Due focus came to be placed on multinational trials with developing countries as partners. In the next section I will look at how the global clinical research community responded to the many instances of unethical research being conducted in developing countries.

2.2. Global response to off-shoring of clinical trials

Born from the history of abuses in human subject research,²⁵ The Declaration of Helsinki (DoH), originally issued by the World Medical Association (WMA) in 1964,²⁶ has undergone seven revisions with the most recent one in 2013. With every revision of the Declaration newer ethical obligations were added depending on the

²² French (1997), *supra* note 16; CNN Web, 'Dangerously flawed' AIDS research criticized: It's Tuskegee Part II, consumer group alleges, (April 22, 1997).

²³ M. Angell, *The Ethics of Clinical Research in the Third World*, THE NEW ENGLAND JOURNAL OF MEDICINE, Vol. 337 (1998).

²⁴ Government of Gambia / Medical Research Council Joint Ethical Committee, *Ethical Issues Facing Medical Research in Developing Countries*, LANCET, Issue No. 351, Issue No. 9098, (1998), pp. 286-287.

²⁵ For a concise historical timeline of research ethics since 1932, see D. B. Resnik, *Research Ethics Timeline* (1932-Present) available at <https://www.niehs.nih.gov/research/resources/bioethics/timeline/index.cfm> (last accessed July 27, 2018)

²⁶ World Medical Association (WMA), Declaration of Helsinki, adopted at 18th WMA General Assembly, May 1964.

technological and methodological advancements in biomedical research. Despite it not being a legally binding instrument, the DoH is considered the most influential instrument in biomedical research ethics alongside the Nuremberg Code (which is discussed in the next Chapter). The first three revisions to the DoH were general revisions, but the fourth revision in 1996 was undertaken in the aftermath of the AZT trial controversy.

It must also be noted that a few years before the AZT controversy in 1993, the Council for International Organizations of Medical Sciences (CIOMS), which was established jointly by the World Health Organization (WHO) and the United Nations Educational, Scientific and Cultural Organization (UNESCO) in 1949, released the updated International Ethical Guidelines for Health-Related Research Involving Humans (hereafter CIOMS guidelines).²⁷ These guidelines stated that “the ethical standards applied [in other countries] should be no less exacting than they would be in the case of research carried out in [sponsoring or trial initiating] country”²⁸ Critics of the AZT trials asserted that since the AZT 076 regimen was the *de facto* standard of care in the developed countries it ought to have been the standard of care given to trial participants in the AZT trials in the low and middle income research sites. They argued that since the trial sponsors neglected to afford the participants on placebo the best *proven* standard of care (as opposed to the best available)²⁹, they had violated the CIOMS ethical guidelines.³⁰

The WMA took note of this criticism and in its fourth revision in 1996 added the phrase “[t]his does not exclude the use of inert placebo in studies where no

²⁷ CIOMS today includes 45 international, national, and member organizations that represent varied biomedical disciplines, national academies of sciences, and medical research councils. CIOMS released a new version of its International Ethical Guidelines for Health-Related Research Involving Humans in 2016, available at <https://cioms.ch/shop/product/international-ethical-guidelines-for-health-related-research-involving-humans/> (available for free download) (last accessed July 27, 2018)

²⁸ CIOMS Guidelines, 1993, Guideline 11: Selection of pregnant or nursing (breastfeeding) women as research subjects, available at <http://www.codex.vr.se/texts/international.html> (last accessed July 27, 2018).

²⁹ Whether the standard of care to be given to participants was the best *proven* or the best *available* was another debate started by the AZT trials. While the critics said that it ought to have been the best proven, the supporters of the trials said that it ought to have been the best *locally available* considering the fact that during the course of these trials most of these countries had no access to the AZT drug priced at around \$800-\$1000 in the US. See R. Levine, *International codes of research ethics: current controversies and the future*, INDIANA LAW REVIEW, Vol. 35, Issue No. 2, (2002), pp. 557-567.

³⁰ Lurie & Wolf, (1997), *supra* note 15.

proven diagnostic or therapeutic method exists” to Article II.3 of DoH that said “[i]n any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method.” However, this addition was not acceptable to some states and the US Food and Drug Administration, for example, has not accepted the changes, continuing to refer to the previous versions of DoH in its reports.³¹

With calls to revise the Declaration again,³² the fifth revision in 2000, along with other structural changes and additions,³³ introduced the idea of distributive justice by shifting the scope from the individual to the community on the whole. The new Article 19 stated that “research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research”. Article 29 stated “[t]he benefits, risks, burdens and effectiveness of a new method should be tested against those of the *best current* prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where *no proven* prophylactic, diagnostic or therapeutic method exists” [my emphasis]. Since discussions on the ethics of placebo-controlled trials are beyond the scope of this thesis, it is sufficient to say that scholars have usually interpreted this Article depending on whichever ethical position they support on placebo-controlled trials.³⁴ In the same revision, Article 30 of the DoH courted further controversy when it introduced the idea of post-trial access to the trial drugs to the research participants. It said that “[a]t the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the

³¹ R. Temple, *Impact of the Declaration of Helsinki on Medical Research from a Regulatory Perspective*, Address to the Scientific Session, WMA General Assembly, September, Helsinki (2003).

³² R. J. Levine, *The need to revise the Declaration of Helsinki*, THE NEW ENGLAND JOURNAL OF MEDICINE, Vol. 341, Issue No. 7, (1999), pp. 531-534.

³³ The document was completely restructured with the introduction rewritten. The new version addressed the vulnerability of healthy volunteers, removed the distinction between therapeutic and non-therapeutic research to make its principles more general, increased the scope of ethical review to include human tissue and data, accepted the necessity to challenge accepted care, and established the primacy of the ethical requirements over laws and regulations. See also R. V. Carlson, et al., *The revision of the Declaration of Helsinki: past, present and future*, BRITISH JOURNAL OF CLINICAL PHARMACOLOGY, Vol. 57, Issue No. 6, (2004).

³⁴ Carlson, et al., (2004), *Id.* These positions fall within three ranges: active-control orthodoxy, placebo orthodoxy, and the middle ground. See further E.J. Emanuel & F. G. Miller, *The ethics of placebo-controlled trials - a middle ground*, THE NEW ENGLAND JOURNAL OF MEDICINE, Vol. 345, Issue No. 12, (2001).

study.” Critics thought that this placed an unfair burden on the research sponsors, while the supporters argued that trial subjects were owed their dues because participants are usually worse off after a trial than they were before.³⁵

Even after the new additions the debates regarding these were far from settled.³⁶ Notes of clarification were added to Articles 29 and 30 in 2002 and 2004 respectively. The WMA resignedly (and allegedly under pressure from the US)³⁷ took a middle ground on placebos and outlined circumstances under which they would be ethically acceptable.³⁸ The clarification on the issue of post-trial care came as something that ought to be considered and not an absolute requirement from the sponsors. Despite these clarifications the debates on these two paragraphs (now paragraphs 33 and 34 in the latest version of the DoH) raged on.³⁹

But the most important change, at least for the purposes of this thesis, brought about in the fifth revision of the DoH, was the addition of Paragraph 9, which reads:

Research investigators should be aware of the ethical, legal and regulatory requirements for research on subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

To understand its importance this paragraph must be distinguished from the paragraph that was included in all the previous versions of the DoH, the previous versions said:

³⁵ Carlson, et al., (2004), *supra* note 33.

³⁶ J. R. Williams, *The promise and limits of international bioethics: Lessons from the recent revision of the Declaration of Helsinki*, INTERNATIONAL JOURNAL OF BIOETHICS, Vol. 15, Issue no. 1, (2004), pp. 31-42.

³⁷ J. Blackmer & H. Haddad, *The Declaration of Helsinki: An Update on Paragraph 30*, CANADIAN MEDICAL ASSOCIATION JOURNAL, Vol. 173, Issue No. 9, (2005), p. 1052.

³⁸ Emanuel & Miller (2001), *supra* note 34; P. Huston & R. Peterson, *Withholding Proven Treatment in Clinical Research*, THE NEW ENGLAND JOURNAL OF MEDICINE, Vol. 345, Issue No. 12, (2001), pp. 912-914.

³⁹ H. Wolinsky, *The Battle of Helsinki: Two troublesome paragraphs in the Declaration of Helsinki are causing a furor over medical research ethics*, EMBO REPORTS, Vol. 7, Issue No. 7, (2006), pp. 670-672. Around this time many other also began questioning the relevance of DoH by calling it out of touch with contemporary clinical realities. See R. Lie, et al., *The standard of care debate: the Declaration of Helsinki versus the international consensus opinion*, JOURNAL OF MEDICAL ETHICS, Vol. 30, Issue No. 2, (2004), pp.190-193.

It must be stressed that the standards as drafted are *only a guide* to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries. [My emphasis]

While the framers previously regarded the DoH as a guidance document which could not supersede national regulations, the revision claimed the DoH to be an authority on the minimum set of international standards that are binding on research investigators worldwide. With the addition of this paragraph, the WMA and the revisers of the DoH have attempted to convert an ethical code into (soft) law, their intent belying their subsequent statement on the relationship between law and ethics:

In some cases the law mandates unethical conduct. The fact that a physician has complied with the law does not necessarily mean that the physician has acted ethically. When the law is in conflict with medical ethics, physicians should work to change the law. In circumstances of such conflict, ethical responsibilities supersede legal obligations⁴⁰

Perhaps not much must be read into the phrasing of Paragraph 9 (Para 10 in the latest version) of the DoH, but it does speak to the complicated relationship between law and ethics. This relationship is explored in detail for the principle and doctrine of informed consent in this thesis. Law and ethics are quite distinct, although interconnected, fields. Paragraph 9 shows that the revisers of the DoH forgot these differences when they reframed the status of DoH as binding *upon* (instead of merely *guiding*) research investigators world over.

In the most recent (seventh) revision to the DoH in 2013, the revisers (i.e. the revision committee members of the World Medical Association)⁴¹ added other provisions relevant to clinical research in developing countries. For the first time, the DoH included the requirement for research participants who are injured during the

⁴⁰ World Medical Association (WMA), *WMA Council Resolution on the Relation of Law and Ethics*, Adopted at 164th WMA Council Session, Divonne-les-Bains, France, (May 2003), available at <https://www.wma.net/policies-post/wma-council-resolution-on-the-relation-of-law-and-ethics/> (last accessed on July 28, 2018)

⁴¹ World Medical Association (WMA) is an independent confederation of National Associations of Physicians and claims to represent Physicians worldwide. Its membership details including details of the revisers is available at <https://www.wma.net/who-we-are/members/>

course of a trial to be treated and compensated.⁴² The new version also calls for greater protection of vulnerable groups, increased measures to inform trial participants of the results of the study, and access to any beneficial treatments that emerge from the research studies.

The multiple revisions of the DoH have led some to question the relevance of the Declaration.⁴³ After the 2000 revision, the US refused to accept any further revisions of the DoH and continues to cite the 1989 version in its reports. In 2006 it announced that it would eliminate all references to the Declaration. Good to its word, the US FDA issued a formal rule that replaced the DoH with Good Clinical Practices (GCP) in 2008.⁴⁴ GCP guidelines were a product of harmonisation of regulatory requirements between EU, Japan, and the US. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is a project that brings together the regulatory authorities of the three countries and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of pharmaceutical product registration. GCP is the international quality standard that focuses on detailing the procedure of a clinical study, including such details as quality standards on clinical protocol, ethical reviews, training, record keeping, and trial facilities including computers and software. It also provides for quality assurance and inspections to ensure that these standards are achieved.

Scholars have argued that the GCP is a less morally authoritative document than the DoH because it remains silent on issues like restrictions on placebo, post-trial access to treatment, benefit of populations of research sites, public disclosure of study design, publication of negative results, and disclosure of conflict of interest.⁴⁵ However, the criticism seems a bit unfair as the document is not meant to merely

⁴² Paragraph 15, WMA, Declaration of Helsinki, (2013), available at <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/> (last accessed July 28, 2018)

⁴³ E. J. Emanuel, *Reconsidering the Declaration of Helsinki*, LANCET, Vol. 381, (2013), p. 1532-1533.

⁴⁴ Department of Health and Human Services, Food and Drug Administration, 21 CFR Part 312, [Docket No. 2004N-0018] Human Subject Protection; Foreign Clinical Studies Not Conducted Under an Investigational New Drug application, Final Rule April 28 2008, effective October 27 2008, available at <https://www.gpo.gov/fdsys/pkg/FR-2008-04-28/pdf/E8-9200.pdf> (last accessed July 28, 2018)

⁴⁵ J. Kimmelman, et al., *Helsinki Discords: FDA, Ethics, and International Drug Trials*, LANCET, Vol. 373, Issue no. 9657, (2009), pp. 13-14; L. HUBERT & H. WAINER, *A STATISTICAL GUIDE FOR THE ETHICALLY PERPLEXED*, (CRC Press, 2013), p. 427.

communicate ethical principles but to lay down procedures pertaining to modalities involved in clinical research and to harmonize regulatory requirements. These modalities are derived from the ethical principles, for instance, the GCP standards on informed consent and responsibilities of investigators are firmly rooted in ethical principles. In fact the GCP standards seem to have more acceptances into national regulatory systems than the DoH, which is mostly referred to as the influence behind the national ethical guidelines along with the Nuremberg Code. The GCP standards have been adopted (with or without minor revisions) by many regulatory authorities in the world (including India's CDSCO).⁴⁶ This is also the case because both the US and EU expect the clinical trial data received from trial sites in third countries to abide by the GCP and Good Manufacturing Practice (GMP) standards for market authorisation of the trialled products.

In the European Union (EU), the requirements for the conduct of clinical trials, including GCP and GMP and their inspections, were implemented in the GCP Directive (Directive 2005/28/EC) and the Clinical Trial Directive (Directive 2001/20/EC, hereafter CTD) which was replaced by the Clinical Trial Regulation (CTR) in 2014.⁴⁷ The CTR provides that clinical trials conducted in third countries that provide data used in an application for market authorisation in the EU are subject to standards (like GCP and GMP) that are *equivalent* to (which is notably different than being the *same as*) those applicable in the Member States under the CTR.⁴⁸

The CIOMS guidelines have also undergone revisions since they first came out in 1982. Revisions were made in 1993, 2002 and, most recently in 2016. The 2016 revisions pertaining to developing countries include the obligation upon research sponsors to make available the interventions that are proven to be effective in research as part of a more general obligation to care for research participants' health needs (Guideline 6). This general obligation also requires that the researchers

⁴⁶ Clinical research information on each country including guidelines and regulatory systems is available at <https://www.nihcollaboratory.org/sites/CbyC/SitePages/Home.aspx>

⁴⁷ Council of the European Union, Regulation (EU) 536/2014 of the European Parliament and of the Council of 16 April 2014 on Clinical Trials on Medicinal Products for Human Use, and Repealing Directive 2001/20/EC, Official Journal of the European Union, L158, (2014), pp. 1-76. (hereafter CTR)

⁴⁸ Article 25(5) CTR, *Id.*

and sponsors make adequate provisions to transition participants who need treatment after their participation in research to appropriate health care services.⁴⁹

But perhaps the most important change made to the Guidelines was that the CIOMS finally recognised that:

Low-resource settings should not be interpreted narrowly as low-resource countries. These settings might also exist in middle- and high- income countries. Moreover, a setting can change over time and no longer be considered low-resource.⁵⁰

This guideline particularly applies to the discussions and underlying ethos of this thesis. The thesis recognises that some aspects of the clinical research industry in India mirror those of high-income countries, while some aspects are similar to low-resource settings. The ethical problems with comprehension, reduced autonomy, healthy volunteers in need of money, etc., faced by research participants and research investigators while dealing with informed consent in India have been similar to (if not entirely the same) to those faced by these stakeholders in high income countries. Therefore, a conscious decision underlies the analytical framework chosen for this thesis, which excludes critical literature on off-shoring of clinical research to the global south. I will discuss these exclusions and explain the scope of this thesis in the next section.

2.3. Scope of the thesis: how it fits in the global and what it excludes

Having outlined the more general, more global, background, it is important to note that the thesis engages with a more limited question, namely: What are the differences between informed consent as outlined in the academic literature and regulatory framework and informed consent as understood by practitioners involved in human subject research in India?

The question evidently suggests the focal point of the thesis is informed consent and that is why most generic debates on clinical research in developing countries or globally have been kept outside the scope of this thesis. If one merely

⁴⁹ CIOMS guidelines (2016), *supra* note 27, Guideline 2, p. 3.

⁵⁰ *Id.*

skims through the literature on consent, one would find that informed consent is a fairly large topic in and by itself, and it has taken some discipline to contain the subject matter of this thesis. The focus is solely on informed consent - the principle, the doctrine, and the practice of it within a given context. And when I use the word context, I mean the clinical research context in India and not *just any* developing country context. This is because I am wary of generalising the findings of this thesis to countries that are economically, socially, or politically similar to India. Moreover, some of the generic literature on “informed consent in developing countries” has been used to contrast the findings from this thesis as a cautionary tale against generalisations pertaining to the global south.

There are many interesting themes and modes of analysis that this thesis could have explored and used, but owing to space constraints some strategic choices had to be made. To keep the thesis focused on informed consent every effort has been made to eliminate discussions not relevant to informed consent. Although many interesting themes within informed consent were also left unexplored, there were a few outside of it, existing on the periphery, which need to be mentioned to show how this thesis fits within the larger debates.

2.3.1. On the periphery

Some peripheral themes inform the global debates that take place around ethical issues in clinical research. The work done in this thesis could potentially serve as a footnote in the larger texts on the following:

i) Critical scholarship

The literature on the political economy of clinical trials has been explicit about the links between pharmaceutical neoliberalism⁵¹ and the recruitment of vulnerable population groups into potentially exploitative regimes of for-profit

⁵¹ Defined sometimes as ‘medical neoliberalism’, which according to Fisher is a political and economic agenda that exhibits two main characteristics, i) where individual choice is prioritised over equity and access, and ii) where health is commodified to transform individuals from patients to consumers. See J. A. Fisher, *Coming Soon to a Physician Near You: Medical Neoliberalism and Pharmaceutical Clinical Trials*, HARVARD HEALTH POLICY REVIEW, Vol. 8, Issue No. 1, (2007).

experimentation.⁵² Fisher holds that the practice of contract research, in which an individual medical practitioner or an organisation takes on trial contracts on behalf of a pharmaceutical corporation, is directly motivated by the effects of neo-liberal reform on the health care system as a whole.⁵³ Contractual trial work is often an alternative form of income for medical practitioners with diminishing sources of revenue. This is fairly common in the US where uninsured or underinsured patients often represent one variety of high-risk and casual labour amongst other vulnerable groups for whom trial participation may possibly be the only means of access to health care.⁵⁴

The pharmaceutical industry has also had to work hard to maximise the advantages that they receive from the neoliberal health reforms of decentralisation and privatisation. Cooper takes note of the routine complaints by the pharmaceutical industry about the high costs of contract work in US and Europe, the time spent in recruiting suitable participants, the high drop-out rates, lack of clinical readability, and non-compliance.⁵⁵ She comments that the neo-liberal hallmarking of the de-collectivization of labour and flexibilities of sub-contracting have ironically also posed the problem of excessive flexibility and fewer ways of confining it. This is why even when the pharmaceutical industry has intensified its outsourcing contracts (with medical practitioners and CROs) in the US and Europe, the drive to push clinical trials offshore is perhaps a way of resolving the dilemma of excessive reliance on unpredictable casual labour in the more advanced economies.⁵⁶ As it is, the “ready-to-recruit”⁵⁷ population groups in developing countries seem to come at a lesser political and economic cost than those in developed ones.⁵⁸

For Petryna, the trial work outsourced to CROs in developing countries is

⁵² K. Sunder Rajan, *Experimental Values: Indian Clinical Trials and Surplus Health*, NEW LEFT REVIEW, Vol. 45, (2007).

⁵³ Fisher (2007), *supra* note 51.

⁵⁴ M. Shuchman, *Commercializing clinical trials risks and benefits of the CRO boom*, THE NEW ENGLAND JOURNAL OF MEDICINE, Vol. 357, Issue No.14, (2007), pp. 1365-1368.

⁵⁵ M. Cooper, *Experimental Labour – Offshoring clinical trials to China*, *East Asian Science, TECHNOLOGY AND SOCIETY: AN INTERNATIONAL JOURNAL*, Vol. Issue No. 2, (2008), pp.73–92.

⁵⁶ *Id.*

⁵⁷ J. A. Fisher, “Ready-to-Recruit” or “Ready-to-Consent” Populations?: *Informed Consent and the Limits of Subject Autonomy*, QUALITATIVE INQUIRY, Vol. 13, Issue No. 6, (2007)

⁵⁸ Cooper (2008), *supra* note 55. See generally, J. A. FISHER, *MEDICAL RESEARCH FOR HIRE: THE POLITICAL ECONOMY OF PHARMACEUTICAL CLINICAL TRIALS*, (Rutgers University Press, 2009).

problematic for the “ethical variability” approach employed in their ethical reviews. She says:

The new clinical trial environments that CROs help to tailor are adaptable, mobile and to some extent, parasitic...Ethics and method are modified to fit the local context and experimental data required. And this ‘ethical variability’ becomes the core value and a presumed course of action in the global testing of pharmaceuticals.⁵⁹

The CROs responsible for recruiting participants for multisite trials are often accused of utilizing variability and uncertainty in the enactment and execution of laws to become “data production sweatshops”⁶⁰ for the pharmaceutical industry. In fact ethical reviews are generally lamented across the political economy scholarship for:

[T]he narrow focus on individual “autonomy” and choice” and the bureaucratization of ethical review, [due to which] structural inequalities tend to fall beyond the purview of ethical scrutiny.⁶¹

Petryna's groundbreaking anthropological work on the outsourcing of clinical research to CROs showed that situations of health crisis could turn into opportunities for pharmaceutical companies to bypass regulatory systems and gain access to research participants whose lack of treatment history (along with lack of education and resources) makes them more likely to produce “cleaner results”.⁶²

Sunder Rajan, who theorises extensively from his anthropological work in India, looks at GCTs through the lens of appropriation and exploitation of bodily potential by global capital. He argues that multisite trials conducted on poorly informed vulnerable population groups in India could “legitimately be seen as

⁵⁹ A. Petryna, *Clinical Trials Offshored: On Private Sector Science and Public Health*, BIOSOCIETIES, Vol. 2, (2007), pp. 21-40.

⁶⁰ P. Azoulay, *Agents of Embeddedness*, National Bureau of Economic Research, Working Paper No. 10142, (December 2003).

⁶¹ J. Dixon & M. Tameris, *Clean Blood, Religion, and Moral Triage in Tuberculosis Vaccine Trials*, MEDICAL ANTHROPOLOGY, (2018) (Published Online) DOI:10.1080/01459740.2018.1463528. Dixon and Tameris refer to the works of the following authors to criticise the narrow focus of ethical reviews which ignore structural inequalities: P. W. Geissler, *Public secrets in public health: Knowing not to know while making scientific knowledge*, AMERICAN ETHNOLOGIST, Vol. 40, Issue No. 1, (2013), pp. 13-34; A. PETRYNA, *WHEN EXPERIMENTS TRAVEL: CLINICAL TRIALS AND THE GLOBAL SEARCH FOR HUMAN SUBJECTS*, (Princeton University Press, 2009); Wendland (2008), *supra* note 13.

⁶² PETRYNA (2009), *Id.*

Western exploitation of Indian bodies”.⁶³ He asserts that the global proliferation of pharmaceuticals has restructured the economic value of health. Patients who are seen as possible consumers of newer therapies and treatments are exploited for their “surplus health”, meaning that their health is no longer the basis for a workforce but rather for pharmaceutical capital.

This thesis has some data that could interest some critical scholars who work on clinical research in India. In the conclusion of the thesis, when talking about issues beyond informed consent, I show how some findings of this thesis can be interpreted within different frameworks. However, it is important to understand that this thesis is not necessarily concerned with globalised clinical research; the trials conducted by some investigators interviewed in this thesis were entirely home-grown trials (with no external sponsors or collaborators). The trial participants interviewed for this research were also appearing for Indian trials and not for the multinational ones. To put it simply, this thesis is not about ‘globalised clinical research’ but about ‘clinical research in India’, which includes some multinational trials. For this reason most critical scholarship on *globalised* clinical research has been kept outside the scope of this thesis.

ii) Wider Clinical Research Ethics

There are many other ethical issues in clinical research in developing countries, like those of placebo-controlled trials, ethical variability in ethical reviews, post-trial access to trialled and proven drug, publication of negative results, etc., all of which are as equally important as questions of informed consent. Yet these have been left outside the scope of the thesis because they are independent issues; the discussions on these do not have much bearing upon the questions on informed consent that this thesis seeks to address. As noted in the introductory chapter, in order to understand the reasons why a series of unethical trials with problematic informed consent procedures have taken place in India in the past few years, the thesis focuses at the heart of the problem. The intention here is to identify the normative content of informed consent and to look at how the practice of it in India deviates or matches

⁶³ K. SUNDER RAJAN, *PHARMOCRACY: VALUE, POLITICS, AND KNOWLEDGE IN GLOBAL BIOMEDICINE*, (Duke University Press, 2017), p. 272.

our theoretical understandings of consent. Moreover, these broader issues in clinical research in developing countries are almost entirely ethical in nature. Informed consent, on the other hand, traverses three domains - that of ethics, law, and practice - and that makes it arguably the most contentious topic in the Medical Law and Ethics literature.

iii) International Normative Instruments

This thesis predominantly looks at the legal doctrine of informed consent as it developed through case law. It forgoes lengthy discussions on international normative instruments on clinical research like the Nuremberg Code, the Declaration of Helsinki, CIOMS guidelines, ICH GCP and GMP standards, and the Universal Declaration on Bioethics and Human Rights. This, however, does not imply that the international normative instruments have had no impact on the development of the legal doctrine of informed consent in clinical research, particularly in India. In fact the developments and updates in the international normative instruments have been reflected in the regulatory requirements and the ethical guidelines pertaining to human subject research in India.

Other than the internationally mandated requirement of informed consent and its usual requirements reflected in the Indian regulatory framework, Paragraph 15 of the Declaration of Helsinki and Guideline 14 of the CIOMS Guidelines also require research participants to be given appropriate compensation for trial-related harm. This requirement is now treated as a legal mandate in Schedule Y of the Indian Drugs and Cosmetics Rules, 1945.⁶⁴ The Rules place the responsibility upon the trial investigator to inform the trial participants of their right and on the procedure to receive compensation upon injury or death. This is now treated as an essential informational requirement for the process of informed consent. While the scope of trial-related harms has not been specified in either the Declaration of Helsinki or the Indian Drugs and Cosmetics Rules, it has been given some substance in Guideline 14

⁶⁴ This was included Schedule Y of the Drugs and Cosmetics Rules, 1945 post the SAM case vide notification G.S.R.53(E), Drugs and Cosmetics (First Amendment Rules), 2013.

of CIOMS and Section 2.6 of ICMR Guidelines⁶⁵ as physical, psychological, legal, economic, or social harms that occur as a consequence of interventions performed solely to accomplish the purposes of research.⁶⁶ The Indian law does not define the scope of harm (which is problematic for fixing liabilities) but mention of the disclosure of compensation during the informed consent process shows that it is responsive to updates in the international normative instruments on clinical research.

Nevertheless, this thesis is not concerned with detailing the legal framework of informed consent or how international normative instruments have impacted the Indian regulatory requirements on informed consent. Such information is easily available⁶⁷ and adds little to the existing knowledge on informed consent.⁶⁸ This thesis looks at all legal avenues that make it possible to bring a claim of lack of informed consent in India. Given the jurisdiction-specific nature of this research it was important to discuss the law of informed consent as applicable to India, the lacunae therein, and the manner in which aggrieved parties could claim sufficient remedy for lack of informed consent in research. In Chapter 4 the thesis shows an absence of a well-defined legal doctrine to deal with a lack of informed consent in research in India. Chapter 4 demonstrates that a legal doctrine is in its early stage of

⁶⁵ Indian Council of Medical Research, National Ethical Guidelines for Biomedical and Health Research Involving Human Participants (October 2017), available at https://www.icmr.nic.in/sites/default/files/guidelines/ICMR_Ethical_Guidelines_2017.pdf (last accessed 28/06/2018)

⁶⁶ CIOMS Guidelines, (2016), *supra* note 27, Guideline 14, p. 55.

⁶⁷ See generally O. V. Nandimath, *Consent and Medical Treatment: The legal paradigm in India*, INDIAN JOURNAL OF UROLOGY, Vol. 25, (2009); Negri, *The Right to Informed Consent at the Convergence of International Biolaw and International Human Rights Law*, In: S. NEGRI, SELF-DETERMINATION, DIGNITY AND END-OF-LIFE CARE, (Brill: Leiden, The Netherlands, 2011); A. M. Capron, *Where Did Informed Consent for Research Come From?*, THE JOURNAL OF LAW, MEDICINE & ETHICS, Vol. 46, Issue No. 1, pp. 12-29; J. F. Merz, *The Nuremberg Code and Informed Consent for Research*, JOURNAL OF AMERICAN MEDICAL ASSOCIATION, Vol. 319, Issue No. 1, (2018), pp. 85-86; J. P. Vandenbroucke & J. Olsen, *Informed Consent and the New EU Regulation on Data Protection*, INTERNATIONAL JOURNAL OF EPIDEMIOLOGY, Vol. 42, Issue No. 6, (2013); See also A. Krajewska, *International Biomedical Law in Search for its Normative Status*, Revista de Derecho y Genoma Humano [Law and the Human Genome Review], Vol. 36, (2012), pp. 121-146; P. G. Moreno & Y. Joly, *Informed consent in International Normative Texts and Biobanking Policies*, MEDICAL LAW INTERNATIONAL, Vol. 15, Issue No. 4, (2015).

⁶⁸ In order to add something new and of value to the academic literature on informed consent this thesis attempts to be less descriptive and more analytical. The analytical framework has been adopted to best tell the story of the place of informed consent within India's clinical research paradigm. Furthermore, in terms of the normative impact of research a discussion on "which legal position must the Indian courts take on informed consent" seems to be greater than discussing "the role of international normative instruments on Indian regulatory system" as issues in clinical research in India have recently reached Indian courts and there is lack of precedent on such issues.

development by charting the Anglo-American case law on informed consent in clinical research. This is done to show possible recourse for an Indian court when handling a claim arising out of a lack of informed consent in research given that Indian courts often rely on Anglo-American precedents to determine legal positions.

Some might critique the reliance on Anglo-American case law for determining cases in India owing to the differences in health care and clinical research systems between India and the US/UK. But such critique overlooks the fact that courts determine *when* informed consent was violated given certain circumstances, as in *when* a person's autonomy, bodily integrity, and dignity were violated owing to what *action or omission* of a clinical researcher (or sponsor) and *what* is owed to the aggrieved party. How advanced or poor a health care or clinical research system is, is irrelevant to determining *when* informed consent is deemed to be violated (see further discussion in Chapter 4). Furthermore, despite the social, economic, and political conditions of other common law countries being different than India, Indian courts have often cited foreign legal precedents while pronouncing progressive decisions on Constitutional and fundamental rights.⁶⁹ Social, political, and economic conditions have almost always been different in India than in countries

⁶⁹ Indian courts have frequently cited decisions from other common law jurisdictions, increasingly so from the US than from the UK, when domestic legal position has been unclear. For instance, when the Supreme Court of India dealt with a case [Kharak Singh v. State of Uttar Pradesh, (1963) A.I.R. S.C. 1295] involving unauthorized police surveillance, based on the facts presented, it held that such surveillance was a violation of the right to privacy. While upholding this right, the Supreme Court relied on many decisions of the U.S. Supreme Court [Wolf v. Colorado, 338 U.S. 25 (1949); Munn v. Illinois, 94 U.S. 113 (1876); Bolling v. Sharpe, 347 U.S. 497 (1954)]. The political and social conditions in India were very different than those in the US at that time and privacy is understood differently in India than elsewhere owing to community-oriented norms. Nonetheless the Court relied on these US precedents to uphold a fundamental right of the citizens. In another case involving freedom of the press [Bennett & Coleman v. Union of India, A.I.R. S.C. 106 (1973)] the Indian Supreme Court relied on the U.S. Supreme Court's decision in Kovacs v. Cooper [336 U.S. 77 (1949)] despite the differences in the political contexts in the two countries as India was on the brink of an Emergency at the time. And this is arguably not one of the progressive decisions that I talk about in the text, but for the sake of argument, the Indian Supreme Court relied on the US cases of Furman v. Georgia, Arnold v. Georgia, and Proffitt v. Florida [408 U.S. 238 (1972); 224 S.E.2d 386 (Ga. 1976); 428 U.S. 242 (1976) respectively] while upholding capital punishment for rarest of the rare cases. This despite the fact that Indian religious context does not support capital punishment in any form. And most recently the Indian Supreme Court decriminalised homosexuality [in Navtej Singh Johar v. Union of India, W.P. (Criminal) No. 76 of 2016] while relying on foreign precedents [Law v. Canada (Minister of Employment and Immigration), 1999 1 S.C.R. 497; Planned Parenthood of South Eastern PA. v. Casey, U.S. 833 (1992); Obergefell, et al. v. Hodges, Director, Ohio Department of Health, et al, 576 US (2015), Lawrence v. Texas, 539 U.S. 558 (2003), amongst many others] despite counter arguments that Indian society was not ready to accept such changes in sexual norms.

whose courts have inspired many legal changes in India.⁷⁰

Ethical principles like informed consent are fundamental to conducting clinical research and protecting the basic rights of a research participant. These rights cannot be simply disregarded because a legal doctrine, based on a universal ethical principle, was developed in a different society. Naturally the differences in cultural and social practices determine how a process, like that of consent, is realised in settings like India, and for that I insist on a case-by-case strategy for tackling cases arising from a lack of informed consent. But the differences in practices or social conditions must not diminish the values that informed consent is in place to uphold.

2.4. Conclusion

This chapter touches upon the larger issues surrounding globalisation of clinical research, but these have been excluded from the analytical framework that is used to answer the principal research question later in the thesis. This chapter explains why this was done while simultaneously acknowledging the larger literature on globalised clinical research which frames the global background to this thesis.

The next chapter brings the focus back on the research question and on informed consent. To identify the normative content of informed consent, the next chapter will discuss the general conceptual framework of informed consent. It will then identify how this conceptual framework fits within the Indian context.

⁷⁰ *Id.*

THE CONCEPTUAL FRAMEWORK WITHIN CONTEXT

3.0. Introduction

This chapter is divided into two parts. Part 1 deals with the idea of informed consent in research. It clarifies the differences between the research and the treatment context, gives a brief history of informed consent in research, and elaborates upon the essential requirements for consent to be ethically and legally valid. Part 2 shows how the conceptual framework fits within the Indian context.

Part 1. The idea of informed consent in research

Before we look at what informed consent entails, it is important to understand the differences between the treatment and the research context. Doing so will help us understand that the process of informed consent varies with the context in which it is carried out.

3.1. Treatment and Research: different contexts

It is common knowledge that while the treatment context deals with the doctor-patient relationship, the research context deals with the relationship between a study investigator/researcher and the research subject who volunteers to be part of a study. Beyond this, the interests, obligations, and technical processes between the two also differ.¹

In treatment, also referred to as the doctor-patient relationship, the doctor owes a primary duty to the patient's well-being. This duty has been termed "personal care".² The primary obligation of a physician is to provide optimal care to the patient in her best interests. But clinical researchers, despite sometimes possessing the best intentions towards their research subjects, have different and competing obligations.

¹ The Encyclopaedia of Bioethics notes that the histories of informed consent in research and in clinical medicine developed largely as separate pieces in a larger mosaic of biomedical ethics, and that these pieces never integrated well despite having developed simultaneously. S. G. POST (ED.), ENCYCLOPEDIA OF BIOETHICS, Vol. 3 (3rd edn., New York: Macmillan Reference USA, 2004), p. 1274.

² C. FRIED, MEDICAL EXPERIMENTATION: PERSONAL INTEGRITY AND SOCIAL POLICY: NEW EDITION (Oxford University Press, 2016), Chapter 3.

Their primary obligation is that their study must generate valid data. If the data so generated is not valid, there was no need to undertake the study in the first place.³ The source of this obligation lies in the ethical justification of clinical research itself. When is it ethically justifiable to put some research subjects at risk of harm in order to benefit others? This question opens the floor to a long-standing philosophical debate, which is outside the scope of this thesis.⁴ Those who hold a utilitarian approach to morality, for example, would (roughly) defend that subjecting participants to harm for research purposes is justifiable when it increases the overall welfare or happiness of a particular society.⁵

Nevertheless, clinical research often involves physicians who act as investigators (physician-investigators) and conduct clinical trials to evaluate experimental treatments in groups of patients who act as subjects of research (patient-subjects). These are the trickier cases for informed consent as the patient-subjects can expect individualised optimal care from the physician-investigator, thereby leading to “therapeutic misconception”. Therapeutic misconception is the failure to appreciate that the elements of a particular research design may limit the degree of individualised care.⁶ Simply put, it means that there is a possibility that the patient-subjects might confuse the goals of research (production of data) with

³ See D. Schatz, *Randomized clinical trials and the problem of suboptimal care: An overview of the Controversy*, CANCER INVESTIGATION, Vol. 8, (1990), pp. 191–205. Of course, this comes with the obligation to not cause harm to the participant, but here I am talking of the primary obligation in terms of the object of the activity.

⁴ The literature on this debate is vast. See for example C. Fethe, *Beyond voluntary consent: Hans Jonas on the moral requirements of human experimentation*, JOURNAL OF MEDICAL ETHICS, Vol. 19, Issue No. 2, (June, 1993), pp. 99-103; A. Schafer, *Experimentation with human subjects: a critique of the views of Hans Jonas*, JOURNAL OF MEDICAL ETHICS, Vol. 9, Issue No. 2, (June, 1983), pp. 76-9; G.O. Schaefer et al., *The Obligation to Participate in Biomedical Research*, THE JOURNAL OF AMERICAN MEDICAL ASSOCIATION, Vol. 302, Issue No. 1, (2009), pp. 67-72; A. L. Caplan, *Is there an obligation to participate in biomedical research?: The Use of Human Beings in Research*, PHILOSOPHY AND MEDICINE, Vol. 28, (1988), pp. 229-248; J. Harris, *Scientific research is a moral duty*, JOURNAL OF MEDICAL ETHICS, Vol. 31, Issue No. 4, (2005), pp. 242-248; R. Rhodes, *Rethinking Research Ethics*, AMERICAN JOURNAL OF BIOETHICS, Vol. 5, Issue No. 1, (2005), pp. 7-28.

⁵ F. G. Miller & D. L. Rosenstein, *The therapeutic orientation to clinical trials*, NEW ENGLAND JOURNAL OF MEDICINE, Vol. 384, Issue No. 14, (2003), pp. 1383–1386.

⁶ P. Appelbaum, et al., *The therapeutic misconception: Informed consent in psychiatric research*, INTERNATIONAL JOURNAL OF LAW AND PSYCHIATRY, 5, (1982), pp. 319–329.

treatment (personal care) and make an uninformed decision.⁷ A situation in which the doctor is the investigator, and where the regular patient of this doctor is also a research subject, could lead to therapeutic misconception. Unlike a clinical trial conducted by clinicians in a research centre or a facility where there is no ongoing doctor-patient relationship between the participant and the investigator of the trial, this situation creates a more complex ethical relationship. Some scholars opine that the therapeutic misconception is often encouraged by ‘a predominant ethical view’ that research initiated by physician-investigators should be conducted with therapeutic intent.⁸ Nevertheless, it is highly improbable that one can conduct good research with a predominant therapeutic intent towards the research subjects. This is because to realise the goals of clinical research, the investigator often acts contrary to the ‘best interests’ of the subjects by concealing important information, depending on the study design.

The treatment context is vastly different from research because in clinical research the need to produce valid data can sometimes override the best interests of the subjects. Lidz has employed some usually found features of clinical trials to illustrate this point further.⁹ The features employed in his analysis are:

- 1) Randomized controlled trials: In such trials, the research subjects (also called trial participants) are assigned a research arm randomly. This is done in trials where the treatments being randomised are in collective equipoise (which means that there is genuine uncertainty in the medical community over which treatment is beneficial).¹⁰ To test which treatment is better, the subjects are

⁷ An uninformed decision based on therapeutic misconception can be counteracted to a certain extent by clear information dissemination and dialogue between the investigator and the research subject, but it is often hard to measure this misconception in real settings. Scholars have opined that there are no adequate measures yet to define and study therapeutic misconception in clinical research settings, see G. E. Henderson, et al., *Clinical Trials and Medical Care: Defining the Therapeutic Misconception*, PLOS MEDICINE, Vol. 4, Issue No. 11, (2007).

⁸ F. Miller & H. Brody, *A critique of clinical equipoise: therapeutic misconception in the ethics of clinical trials*, HASTINGS CENTER REPORT, Vol. 33, (2003), pp. 19–28.

⁹ C. W. Lidz, *The Therapeutic Misconception and our models of competency and Informed Consent*, BEHAVIOURAL SCIENCES AND THE LAW, Vol. 24 (2006), pp. 535–546.

¹⁰ See generally S. J. L. Edwards, *The ethics of randomised controlled trials from the perspectives of patients, the public, and healthcare professionals*, THE BRITISH MEDICAL JOURNAL, Vol. 317, Issue No. 7167, (October 1998), pp. 1209–1212.

randomly assigned different treatment arms. This undermines the interest of the subject as the subject does not get to choose the arm of the treatment and cannot control the potential side effects of the drug that she could have managed.¹¹ In terms of generating data, randomization is only stopped when there is sufficient evidence that one arm of treatment is much superior to the other and future health professionals can base treatment decisions on it.

- 2) Double-blind clinical trials: In such trials, neither the investigator nor the subjects know which subject is going to receive which of the several treatments. The essential condition of informed consent, of giving full information to the research subject, is violated by the very nature of the trial.
- 3) Placebo controlled trials: A placebo is an inactive drug. In such trials, the subjects are given either the active drug or a placebo. Placebo controls are only used if there is no convincing evidence for the effectiveness of standard treatment.¹² They are widely employed to improve the scientific assessment

¹¹ Lidz (2006), *supra* note 9. Lidz writes that some trial participants may have strong preferences for the predictable side effects of one medication or another. For instance, “a young single man with an active sex life may find impotence a much more troubling side-effect than a woman whose sexuality is unaffected by the same medication.”

¹² The ethics of placebo controlled trials have been a subject of intense scrutiny. The CIOMS guidelines lay down that placebo is acceptable “when there is no established effective intervention for the condition under study, or when placebo is added on to an established effective intervention...as a comparator...if there are compelling scientific reasons for using placebo; and if delaying or withholding the established effective intervention will result in no more than a minor increase above minimal risk to the participant and risks are minimized, including through the use of effective mitigation procedures.” Placebo intervention is also justified in trials of new treatments for conditions whose response to both established treatments and placebo is highly variable, for example, anti-depressants have a high placebo response rate and sometimes there is inconsistent evidence on efficacy of such drugs because of it. See E. J. Emanuel & F. G. Miller, *The ethics of placebo-controlled trials-a middle ground*, THE NEW ENGLAND JOURNAL OF MEDICINE, Vol. 345, Issue No. 12, (2001), pp. 915–919; J. Millum & C. Grady, *The Ethics of Placebo-controlled Trials: Methodological Justifications*, CONTEMPORARY CLINICAL TRIALS, Vol. 36, Issue No. 2, (November, 2013), See also Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, (Geneva, 2016), available at <http://www.cioms.ch/index.php/12-newsflash/400-cioms-international-ethical-guidelines> (last accessed on June 2, 2018)

of studies in depression and other psychological disorders, even though medicines for such disorders are widely available.¹³

The above-mentioned features are pointed out not to insinuate that clinical researchers are not inclined to care for the research subjects. Lidz mentioned these features in his essay on therapeutic misconception to prove that the “compromises on personal care that are built into the design of a clinical trial are an important risk that needs to be appreciated” for any trial participant giving a valid informed consent to participate.¹⁴

The demarcation between the two contexts is enormously important to appreciate that despite the same principle operating in both the settings; the overall process significantly varies in both. Most non-therapeutic research involves conducting trials on healthy volunteers (who generally receive no direct medical benefit); and the risk taken by the research subject is oftentimes much higher than in treatment. Due to this aspect of clinical research, not only are the consent forms more elaborate, but the responsibility on investigators to adhere to the essential requirements of informed consent is also stronger.¹⁵ Moreover, the processes in research also vary depending on which aspect of clinical design the study opts for. For instance, the process of taking consent is different for randomisation than for placebo-controlled trials.

¹³ See further W. Carpenter, W, et al., *The declaration of Helsinki and clinical trials: A focus on placebo-controlled trials in schizophrenia*, AMERICAN JOURNAL OF PSYCHIATRY, Vol. 160, Issue No. 2, (2003), pp. 356–362.

¹⁴ Lidz (2006), *supra* note 9.

¹⁵ The consent form for treatment is usually a single page generic document where the diagnosis of the patient is written along with intervention or procedure to be performed by the doctor; this is followed by a declaration and signature from the patient. It does not go through an ethical review. Conversely, the consent form for research is a multi-page document that has to include all the particulars in the form as outlined in the ethical guidelines. This document goes through ethical review and can only be used after passing such review. *see* Essential and additional elements of an informed consent document, in: Indian Council for Medical Research (ICMR), National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017, (hereafter ICMR Ethical Guidelines 2017) p. 50, available at https://icmr.nic.in/guidelines/ICMR_Ethical_Guidelines_2017.pdf (last accessed on June 29, 2018).

Having made the important distinction between the research and treatment context, the discussion on the idea of informed consent can be taken further by briefly looking at the history of informed consent in research.

3.1.1. Tracing the history of informed consent in research

Almost every account of the history of informed consent in research begins with the aftermath of human experimentation in the Second World War and the codes of practice that emerged from the Nuremberg trials.¹⁶ There is evidence of consent-like practices in research prior to the Nuremberg trials, for instance, in Walter Reed's yellow fever experiments.¹⁷ There is also evidence of guidelines existing in Germany in 1931 that were similar in content to the Nuremberg Code,¹⁸ but in this thesis I will adhere to the *modern* (post World War II) understanding and practice of informed consent in research.¹⁹ The Nuremberg Code was set out as part of the judgment in the

¹⁶ R. R. FADEN & T. L. BEAUCHAMP, *A HISTORY AND THEORY OF INFORMED CONSENT*, (New York: Oxford University Press: 1986), p. 152; J. W. BERG, ET AL., *INFORMED CONSENT: LEGAL THEORY AND CLINICAL PRACTICE*, (2nd edn., New York: Oxford University Press, 2001); W. T. REICH (ED.), *ENCYCLOPEDIA OF BIOETHICS*, (Simon and Schuster MacMillan, New York: 1995).

¹⁷ Research shows that the American military had made some significant efforts to ensure voluntary consent in infectious diseases experimentation like those conducted by Army surgeon Walter Reed for yellow fever in the early 1900s. The study involved infecting healthy human volunteers with "loaded mosquitoes", however, these studies included a written contract to be signed by the subject, which is perhaps the first example of written informed consent in research, *see* S. E. LEDERER, *SUBJECTED TO SCIENCE: HUMAN EXPERIMENTATION IN AMERICA BEFORE THE SECOND WORLD WAR*, (Baltimore Johns Hopkins University Press, 1995).

¹⁸ In terms of a written ethical code incorporating informed consent, new research has shown that ethical regulation in the tradition of informed consent was documented prior to the Nuremberg Code. This came in a circular issued by the Reich minister of interior in Germany in 1931 titled "guidelines for new therapy and human experimentation" [translated] which made a clear distinction between therapeutic (new therapy benefiting the participant) and non-therapeutic research (experimentation). This step came after public outcry over the Neisser case, where Albert Neisser conducted serum trials by infecting healthy people with Syphilis to test a vaccine, and other similar unethical cases of experimentation, *see* J. Vollmann & R. Winau, *Informed Consent in Human Experimentation before the Nuremberg Code*, *THE BRITISH MEDICAL JOURNAL*, Vol. 313, Issue No. 7070, (December 1996), pp. 1445-1449. Six of the ten guidelines in the Nuremberg Code are said to be based on the 1931 Guidelines introduced by the Reich, *see* R. B. Ghooi, *The Nuremberg Code – a critique*, *PERSPECTIVES IN CLINICAL RESEARCH*, Vol. 2, Issue No. 2, (2011).

¹⁹ While tracing the history of informed consent in research, Faden and Beauchamp state that despite there being events in research ethics before the end of World War II, rarely any could be deemed significant enough to have had a major impact on later developments, FADEN & BEAUCHAMP (1986), *supra* note 16, p. 151. It seems fitting to mention here that the pre-eminence of the rights and safety of patients has been recognized since the time of Hippocrates. It has been also been supposed that the rights of trial subjects were first enunciated in the context of experimental therapy by Claude Bernard.

case *U.S.A. v. Karl Brandt et al* (also known as the Doctor's Trial),²⁰ in which twenty doctors and three administrators were indicted for organizing and participating in war crimes and crimes against humanity in the form of medical experiments and medical procedures conducted on prisoners and civilians. The Code laid down ten principles of which the first principle reads: "the voluntary consent of the human subject is absolutely essential."²¹ Elaborating the requirement further, it stated:

This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision.²²

It is important to note that no nation or key medical association has officially adopted the Nuremberg Code as law, but it has had a profound influence on the development of international human rights law and medical ethics.²³ The requirement of consent for experimentation was incorporated into Article 7 of the United Nations

See generally W.H.S. JONES, *HIPPOCRATIC CORPUS, OATH AND EPIDEMICS 1, VOLS. 1-2*, [citing Hippocratis Coi Medicorum Omnium Longe Principis, 1555 edition] (Cambridge (MA): Harvard University Press, 1923). *See also* C. BERNARD, translated by HENRY COPLEY GREENE, *AN INTRODUCTION TO THE STUDY OF EXPERIMENTAL MEDICINE*, (2nd edn., New York: Dover Publications, 1957) at p. 102 "Among the experiments that may be tried on man, those that can only harm are forbidden, those that are innocent are permissible, and those that may do good are obligatory...It is immoral then, to make an experiment on man when it is dangerous to him, even though the result may be useful to others. It is essentially moral to make experiments on an animal, even though painful and dangerous, if they may be useful to man". *See generally* P. RABINOW, *ESSAYS ON THE ANTHROPOLOGY OF REASON*, Princeton University Press, 1996), at p. 159, where the author cites Claire Ambroselli's argument that Bernard's conception of experimental medicine was somewhat a mutually non-dissolvable relationship between claims of scientific medicine and those of individual patients.

²⁰ *The United States of America v. Karl Brandt et al.*, November 21, 1946 - August 20, 1947, National Archives and Records Service, General Service Administration, Washington: 1974, available at <https://www.archives.gov/research/captured-german-records/microfilm/m887.pdf> (last accessed on June 2, 2018)

²¹ *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10*, Vol. 2, pp. 181-182, (Washington, D.C.: U.S. Government Printing Office, 1949).

²² *Id.*

²³ M. A. Grodin & G. J. Annas, *Legacies of Nuremberg: Medical Ethics and Human Rights*, *JOURNAL OF AMERICAN MEDICAL ASSOCIATION*, Vol. 276, (1996), pp. 1682-1683. Moreover, the tenets of the Code have recently been incorporated into the UNESCO Declaration on Bioethics and Human Rights adopted in 2005, the most recent international instrument to be adopted at the global stage.

International Covenant on Civil and Political Rights (ICCPR), 1996.²⁴ The Code also became the basis for the Declaration of Helsinki released by the World Medical Association (WMA) in 1964, with the most recent amendment in 2013,²⁵ and the International Ethical Guidelines for Biomedical Research Involving Human Subjects released by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organisation (WHO).²⁶ Both these documents are widely regarded as the cornerstone documents in human research ethics.²⁷ The Nuremberg Code, being a by-product of case law, laid down the moral standards for conducting research on human subjects. The moral standards, though often conceptually debated, are firmly established in the general ethical theory of informed consent, but the legal doctrine has been slow to catch up to the ideal. The next section will lead into this ethical-legal interaction further.

3.1.2. The initial point of departure between legal and ethical approaches

Unlike the above instruments that are formulated based on ethical considerations that relate to informed consent in clinical research, the legal doctrine of informed consent is primarily a creature of case law pertaining to doctor-patient relationships. Not many research-based cases have come before the courts; therefore, the legal doctrine that has developed around the treatment context is often extended to the research context; this caveat is provided to help avoid confusion whenever the treatment context is brought up below while talking about the legal doctrine of informed consent.

²⁴ Article 7, International Covenant on Civil and Political Rights, United Nations Treaty Series, Vol. 999, p. 171.

²⁵ World Medical Association (WMA), Declaration of Helsinki, last amended at the 64th WMA General Assembly, Fortaleza, Brazil, October 2013, available at <http://jamanetwork.com/journals/jama/fullarticle/1760318> (last accessed on June 2, 2018)

²⁶ CIOMS Guidelines, *supra* note 12.

²⁷ B. Snezana, *The Declaration of Helsinki: The Cornerstone of Research Ethics*, ARCHIVE OF ONCOLOGY, Vol. 9, Issue No. 3, (2001), pp. 179–84; B. Hepple, *The Framework of Guidance*, in: B. HEPPLE, *THE ETHICS OF RESEARCH RELATED TO HEALTHCARE IN DEVELOPING COUNTRIES* (A Follow-up Discussion Paper Based on the Workshop Held in Cape Town, South Africa 12-14th February 2004), p. 58; J. V. Lavery, *Putting International Research Ethics Guidelines to Work for the Benefit of Developing Countries*, YALE JOURNAL OF HEALTH POLICY, LAW, AND ETHICS, Vol. 4, Issue No. 2, (2013).

Even though the Nuremberg Code provided for the idea of voluntary and knowledgeable consent in research, the term ‘informed consent’ first appeared in *Salgo v. Leland Stanford Jr. University Board of Trustees* in 1957.²⁸ In this case,²⁹ the California Court of Appeals held that “a physician violates his duty to his patient and subjects himself to liability if he withholds any facts which are necessary to form the basis of an intelligent consent by the patient to the proposed treatment.”³⁰ Regarding the element of risk, pertaining to disclosure that could psychologically or emotionally affect a patient and influence her choice to her detriment, Justice Bray wrote, “in discussing the element of risk a certain amount of discretion must be employed consistent with full disclosure of facts necessary to an *informed consent*”³¹ [my emphasis]. This is how the term ‘informed consent’ was introduced to the world. Ever since its first use in case law governing the doctor-patient relationship, the law of informed consent has almost exclusively focused on treatment rather than the research context. Such exclusivity has led commentators to suggest that the ethical understanding of informed consent seems to do more justice to the context of clinical research than the legal definition, as the former better understands the relational process between the researcher and the research subject.³²

On the other hand, informed consent, from a legal point of view, means that a physician has a duty to inform the patients of the foreseeable risks in treatment and to obtain their consent. This will be detailed in the next chapter, but the gist of it would be that if a patient is injured as a result of a failure on the part of a physician to disclose information about a procedure, then the patient may collect monetary damages from the physician for causing the injury. The focus, evidently, is entirely

²⁸ ENCYCLOPEDIA, p. 1271, *supra* note 1. The term was first used in the case *Salgo v. Leland Stanford Jr. University Board of Trustees*, 54 C.A. 2d 560; 317 P. 2d 170 [1957], *see also* FADEN AND BEAUCHAMP (1986), p. 125, *supra* note 16.

²⁹ In this case the patient was paralyzed from a new diagnostic treatment and argued that the doctor had been negligent in not warning him that there was a risk of paralysis in the treatment. This case was brought on the issue for medical malpractice, but the secondary issue was the breach of duty to inform the patient of all the risks inherent in the treatment.

³⁰ *Salgo* case, p. 181, *supra* note 28.

³¹ *Id.*

³² FADEN AND BEAUCHAMP (1986), *supra* note 16, p. 3; *See also* T. L. BEAUCHAMP, *STANDING ON PRINCIPLES*, (Oxford University Press: 2010), p. 68, where Beauchamp has argued that the heart of informed consent is moral not legal as informed consent has less to do with the liability of professionals and more to do with the autonomous authorization of individuals.

on an inquiry post-injury, fixing liabilities, and compensation. While the ethics of informed consent are universally applicable and guide the entire process of consent, the law of informed consent is territorially defined and normally only deals with post fact remedy. This is primarily the reason for why the legal understanding of informed consent falls behind its ethical underpinnings. The courts rarely ponder over questions of what the idea of voluntariness entails, or whether comprehension is an essential element of informed consent. They consider *material* facts of the case, facts that are crucial to fixing liabilities, and leave the pondering to the theorists. The legal description of informed consent, though effective for remedial purposes, thus fails to capture the relationship between an investigator and a research subject and the context of clinical research. This will become clearer as the thesis progresses. The next few sections will explain the essential features of informed consent by contrasting their understanding in ethics and in law.

3.1.3. The essentials of informed consent

The most important role of informed consent is that it is required to legitimise any intervention done on the human body. But an intervention can only become legitimate when the essential requirements of informed consent are met. A study of literature from various disciplines shows that informed consent has three essential requirements,³³ which are:

- a) Voluntariness,
- b) Adequate Information Disclosure, and
- c) Competence/Capacity

³³ See FADEN AND BEAUCHAMP (1986), *supra* note 16, p. 274; National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, The Belmont Report, Washington, D.C.: Department of Health, Education, and Welfare (DHEW), Publication Number 78-12, (1978), p.10; T. BEAUCHAMP & J. CHILDRESS, *PRINCIPLES OF BIOMEDICAL ETHICS*, (7th edn., New York: Oxford University Press, 2013); A. Meisel & L. Roth, *What We Do and Do Not Know About Informed Consent*, *JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION*, Vol. 246, (November 1981), pp. 2473-77; M. P. Stansfield, *Malpractice: Toward a Viable Disclosure Standard for Informed Consent*, *OKLAHOMA LAW REVIEW*, Vol. 32 (1979): pp. 871-74; L. Alexander, *The Moral Magic of Consent* (II), *LEGAL THEORY*, Vol. 2, Issue No. 1352, (1996); V. Tadros, *Consent to Harm*, *CURRENT LEGAL PROBLEMS*, Vol. 4, Issue No. 23 (2011).

These essential elements are also the parameters on which the validity of consent is measured. The following sections will elaborate each constitutive element of informed consent in order to show that informed consent is not as simple a concept as it appears to be at first glance.

a) Voluntariness

If we were to understand voluntariness in broad legal terms, it would mean an act proceeding from the “free and unrestrained will” of a person.³⁴ Voluntariness is arguably the most frequent ground for the contestation of the validity of informed consent. In medical law, three factors have been identified which serve to vitiate voluntariness in medical contexts: coercion, undue influence, and mistake.³⁵ Each of these factors is important enough to warrant their own themed projects. For the sake of this inquiry, I will not adjudicate between the different theories of these factors. Instead, I will adopt an existing theory, explain why I have adopted it, and show the implications of the theoretical framework adopted.

Faden and Beauchamp note that voluntariness is perhaps the most frequently mentioned principle in the literature of informed consent.³⁶ Frequency, however, does not entail clarity. Much of the literature discussing voluntariness in clinical research comes from philosophers and bioethicists who seek to define and find measures to assess voluntariness.³⁷ For some scholars, voluntariness means consent

³⁴ For instance, the Tennessee Court of Appeal defined a voluntary act as “[o]ne that proceeds from one's own free will, done by one's choice, or one's own accord, unconstrained by external inferences, force or influence, and not prompted or suggested by another”, *Brown v. McCulloch et al.*, 24 Tenn. App. 324 (Tenn. Ct. App. 1940).

³⁵ E. JACKSON, *MEDICAL LAW: TEXT, CASES, AND MATERIALS*, (Oxford University Press, 2009), p. 217. Note that I have kept ‘mistake’ out of the scope of this thesis, as the concept is mostly relevant in the treatment context.

³⁶ FADEN AND BEAUCHAMP (1986), *supra* note 16, p. 7.

³⁷ P. Appelbaum, et al., *Voluntariness of Consent to Research*, HASTINGS CENTER REPORT, (2009), pp. 30-39; C. Pace & E. J. Emanuel, *The Ethics of Research in Developing Countries: Assessing Voluntariness*, THE LANCET, Vol. 365, (2005), pp. 11-12; R. M. Nelson, et al., *The Concept of Voluntary Consent*, AMERICAN JOURNAL OF BIOETHICS, Vol. 11, Issue no. 8, (2011), pp. 6-16; N. E. Kass, et al., *Motivations, Understanding, and Voluntariness in International Randomized Trials*, IRB: ETHICS & HUMAN RESEARCH, Vol. 27, Issue No. 6, (2005), pp. 1-8; Olsaretti, *Freedom, force and choice: Against the rights-based definition of voluntariness*, JOURNAL OF POLITICAL PHILOSOPHY, Vol. 6, (1998), pp. 53-78.

that is “free from controlling influences or conditions”.³⁸ Such a definition not only includes the influence of people, but also the circumstances or conditions that lead to consent. However, this is a point of contention amongst commentators.

Some consider circumstantial influences like those of poverty and lack of access to basic health care as *harsh circumstances*.³⁹ They argue that despite the circumstances having led to the choice made by the participants, it was still their choice. As such, circumstances and conditions should be kept outside the purview of a more helpful definition of voluntariness.⁴⁰ Some scholars bring in the concept of ‘coercion’ while talking about harsh choice circumstances. This concept is useful to understand because consent is generally defined as *voluntary when it is not coerced*; hence, the two concepts are frequently mentioned together. A few commentators argue that some potential research subjects, particularly those in developing countries, are so disadvantaged that large payments given to them would unduly induce them to participate in a clinical trial despite the risks involved. They argue that such offers of payment are potentially coercive.⁴¹ This leads to the conclusion that poor or disadvantaged people are coerced into trial participation through such offers, therefore, their consent becomes non-voluntary, hence, invalid. However, such a notion does not pass the test of coercion. To explain this, I will take Wertheimer’s account of coercion.

Wertheimer proposes, “only *threats* coerce, but not all threats do”.⁴² Under this account, an act is not coercive unless the choice forced upon the coercee leaves her with no reasonable choice but to yield. Wertheimer and Miller have argued that sometimes having no reasonable choice or alternative might naturally be viewed as a

³⁸ *Id.* Nelson et al., (2011), in this article the authors conceptualise voluntariness as intention to consent with the absence of exposure to controlling influences or conditions.

³⁹ J. S. HAWKINS & E. J. EMMANUEL, *EXPLOITATION AND DEVELOPING COUNTRIES: THE ETHICS OF CLINICAL RESEARCH*, (Princeton University Press, 2008), p. 25.

⁴⁰ *Id.*

⁴¹ R. Macklin, *The paradoxical case of payment as benefit to research subjects*, *IRB: ETHICS AND HUMAN RESEARCH*, Vol. 11, (1989), pp. 1–3; T. L. Schonfeld, et al., *Research Involving the Homeless: Arguments against Payment-in-Kind (PinK)*, *IRB: ETHICS AND HUMAN RESEARCH*, Vol 25, Issue No. 5, (September-October 2003), pp. 17– 20; J. McGregor, “*Undue inducement*” as coercive offers, *AMERICAN JOURNAL OF BIOETHICS*, Vol. 5, Issue No. 5, (2005), pp. 24–25.

⁴² A. WERTHEIMER, *COERCION*, (Princeton University Press, 1987), Chapters 2, 12 and 14.

necessary condition for coercion, which it is, but not all offers where people have no reasonable alternatives lead to coercion, as there are no *threats*⁴³ involved. The authors compellingly argue that the need for money does not preclude voluntary consent. According to Wertheimer and Miller, genuine offers do not coerce, and some other prominent theorists in the field have supported this view.⁴⁴ According to the Belmont Report, that is a leading commentary on the rights and protection of research subjects, coercion must include some kind of ‘threat’ of harm which is absent in payment for research participation.⁴⁵ Moreover, English law has maintained that certain unfavourable circumstances (such as being in prison) cannot be said to vitiate consent in medical treatment unless a ‘real threat’ can be determined to have diminished the patient’s free choice.⁴⁶ This includes situations where the political or social context of the patient might significantly alter this range of options.⁴⁷

⁴³ A ‘threat’ is a conditional proposal (‘if’ you do or do not do x, ‘then’ y will follow). According to a moral baseline, if this conditional proposal is rejected by the person, it leaves her worse off. The moral baseline here is that one is generally entitled not to be deprived of one’s liberty. An act against a moral baseline does not mean that it can never be justified, but a special case needs to be made for it. Wertheimer draws a difference between ‘threats’ and an ‘offer’ or ‘inducement’. For instance, in an offer like “if you take this medication, you will receive a payment”, rejection of the proposal does not leave the person worse off or with an unfavourable consequence, as the person is not entitled to a payment. A. Wertheimer, *A philosophical examination of coercion for mental health issues: some basic distinctions: analysis and justification*, BEHAVIOURAL SCIENCES AND THE LAW, Vol. 11, (1993), pp. 239-258.

⁴⁴ Agreeing with the legal notion of coercion which is restricted to visible, intentional, and personal threats, the authors opined that all other pressures “are not, strictly speaking, coercive” enough to render consent invalid, *see* FADEN AND BEAUCHAMP, (1986), p. 338, *supra* note 16.

⁴⁵ A. Wertheimer & F. G. Miller, *Payment for Research Participation: A coercive offer?*, JOURNAL OF MEDICAL ETHICS, Vol. 34, Issue No. 5, (2008). The Belmont report, on which a number of scholars rely for authoritative guidance, also states that, “[c]oercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance”, *see* The Belmont Report, (1978), *supra* note 33.

⁴⁶ “The threat had to be real: vain threats that would not coerce the “constant man” were not enough”, R. J. Sutton, *Duress by Threatened Breach of Contract*, MCGILL LAW JOURNAL, Vol. 20, (1974), citing Cokes Institutes of the Lawes of England from the 1600s, 1 Co. Inst. 253b.

⁴⁷ *See* Freeman v. Home Office (No. 2), [1984] 1 All E.R. 1036. In this case the plaintiff, a prisoner serving a life term, claimed that the prison officials forcibly gave him psychoactive drugs. He claimed that despite him having consented to the administration of drugs, his consent was not legally adequate because he was coerced into consenting due to his status as a prisoner, and that he was not fully informed about the nature of the treatment or the risks involved. The court rejected his claim and ruled that he had consented to the administration of drugs and he had been sufficiently informed of the purpose of the treatment. The court further rejected his claim of coercion noting that imprisonment did not diminish the autonomy of an individual. *See also* FADEN AND BEAUCHAMP (1986), p. 125, *supra* note 16, it seems that the law and ethical theory seem to agree on the definition of coercion, if we

Having discussed coercion as the antonym concept of voluntariness, one still seeks conceptual clarity on voluntariness. This is mainly because the requirement of voluntariness as “free and unrestrained will” sheds light on one of the oldest dilemmas of consent theory and its application. While talking about the applicability of consent theory to politics, the political theorist Kann, wrote the following:

If we are social beings, how can we consent ‘voluntarily’? Do our desires and reasons reveal our ‘true’ selves or do they merely reflect social prejudices? Herbert Marcuse’s challenge that consent procedures are vacuous if our desires and reasons are socially determined is a serious one.⁴⁸

It is easy to dismiss this dilemma as a recondite philosophical inquiry, but the difficulty lies in matching the ideal situation of a consenting individual with the lived realities of actual people. An average individual, while performing an action, is influenced by a web of social and other influences. Therefore, this dilemma has been drawn out in much of the literature on informed consent as well.⁴⁹ A definition of voluntariness, which requires a completely ‘free and unrestrained will’, would mean that very few modern human actions are truly voluntary. Therefore, as impractical as it seems to expect perfectly free will or perfect voluntariness, it should indubitably also mean that perfect consent does not exist.

The crux of this section is that voluntariness is an essential requirement for informed consent, but what the term encompasses and what negates voluntariness in

acknowledge the definition of coercion proposed by Faden and Beauchamp, who write, “[c]oercion occurs if one party intentionally and successfully influences another by presenting a credible *threat of unwanted and avoidable harm* so severe that the person is unable to resist acting to avoid it”. [My emphasis].

⁴⁸ This has been referred to as the ‘dialectic of consent’ in consent theory in politics, which is equally applicable to the discussions around voluntariness in informed consent. M. Kann, *The Dialectic of Consent Theory*, JOURNAL OF POLITICS, Vol. 40, Issue No. 2, (1978), pp. 386 -408, p. 388.

⁴⁹ It has been noted by authors that quite often in academic literature describing informed consent, the focus is generally on theoretical concepts rather on *lived experiences* of the clinicians. For instance it is the modern practice of having physicians as investigators of trials, but most literature on informed consent seems to bypass such developments in practice and sticks to the old notions of treatment and research, see A. HEDGECOE, *THE POLITICS OF PERSONALISED MEDICINE: PHARMACOGENETICS IN THE CLINIC*, (Cambridge University Press, 2004), p. 172. Some philosophers write against having value-free definitions of concepts like voluntariness, this to a certain extent means that lived realities full of value-judgments matter while trying to assess concepts like voluntariness, Wertheimer (2012), *supra* note 16; P. Appelbaum et al., (2009), *supra* note 37.

research, has been the subject of much academic debate. The differing academic opinions make it harder to empirically assess situations that might be considered voluntary. Therefore, I assess my empirical findings in the later chapters keeping in mind the debates that surround its conceptualisation.

As enquiries in bioethics are gearing towards basing themselves in empirical claims, concepts like voluntariness are being remodelled to stand rigorous empirical assessments.⁵⁰ There are no adequate measures of voluntariness yet, but it is a constantly evolving research field.⁵¹ Furthermore, voluntariness is not a stand-alone requirement for valid informed consent. For an act of consent to be voluntary, the person must have reasonably assessed the information about risks and benefits arising out of the study and made a fully informed decision. The requirement of adequate information disclosure and assessing comprehension of that information will be discussed in the following section.

b) Information Disclosure and Comprehension

Adequate information disclosure for valid informed consent means disclosure of all the relevant information that may have an impact on the voluntary decision making of the subject regarding participation in research. The Declaration of Helsinki (as amended in 2013) lays down that:

[E]ach potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal.⁵²

⁵⁰ N. Mamotte & D. Wassenaar, *Measuring Voluntariness of Consent to Research: An Instrument Review*, JOURNAL OF EMPIRICAL RESEARCH ON HUMAN RESEARCH ETHICS, Vol. 10, Issue No. 2, (2015), pp. 121-131; C. A. Pace & E.J Emanuel, *The ethics of research in developing countries: assessing voluntariness*, THE LANCET, Vol. 365, Issue No. 9453, (January, 2005), pp. 11-12.

⁵¹ *Id.*

⁵² The Declaration of Helsinki, Principle 26 (as amended in 2013), *supra* note 25.

Some commentators suggest that it is not realistic to communicate *all* the study details to the potential participants of research.⁵³ The reasons range from the technicality and quantity of the information to the disinterest of the research participants. So how do we determine what information is *adequate* for potential trial participants to make a truly informed decision?

In case law pertaining to treatment (as developed by the English and US courts) the adequacy of information disclosure is assessed on three standards: the professional practice standard, the reasonable person standard, and the - less commonly used - subjective standard.⁵⁴ The professional practice standard holds that the criteria of adequate disclosure are properly determined by the customary practices of the professional medical community.⁵⁵ This standard would imply that the patient or subject is unqualified to determine the adequacy of information required for her to make a decision regarding treatment or research. The reasonable person standard would assess adequacy of information based on what a reasonable person would need to know about a procedure/study, viz., the risks, alternatives, and results.⁵⁶ The subjective patient standard would require the physician to disclose whatever information is material to the particular patient. The legal test of adequate disclosure is 'materiality' of information, meaning what is material or significant to the decision-making of the person. The subjective standard, though often regarded as the standard closest to the ethical ideal, has been criticised for placing an unfair legal burden on physicians to perceive the "idiosyncratic values and interests of their patients and leaving the physicians at the mercy of their patients' self-serving

⁵³ BEAUCHAMP (2010), *supra* note 32; O. O'NEILL, *AUTONOMY AND TRUST IN BIOETHICS*, (Cambridge University Press, 2002); F. J. Ingelfinger, *Informed (but uneducated) consent*, THE NEW ENGLAND JOURNAL OF MEDICINE, Vol. 287, Issue No. 9, (1972), pp. 465–466; L. Katzner, *The Ethics of Human Experimentation: The Information Condition*, in: W. L. ROBISON & M. S. PRITCHARD (EDS.), *MEDICAL RESPONSIBILITY, PATERNALISM, INFORMED CONSENT, AND EUTHANASIA*, (Clifton, X. J. : The Humana Press, 1979), pp. 43–56.

⁵⁴ BEAUCHAMP (2010), p. 67, *supra* note 32,

⁵⁵ The standard, also called the 'Bolam test' was developed in a medical negligence case, the Bolam principle said that "[a] doctor is not guilty of negligence if he has acted in accordance with a practice accepted as proper by a responsible body of medical men skilled in that particular art", *see* Bolam v. Friern Health Management Committee, [1957] 1 W.L.R. 582 (QB).

⁵⁶ The court in Canterbury case said that a physician must disclose all risks which a reasonable person would consider significant in deciding whether to go forward with the procedure, *see* Canterbury v. Spence., 464 F.2d 772 (D.C. Cir. 1972).

hindsight in court”.⁵⁷ Nevertheless, other commentators suggest that the subjective standard would best protect the autonomy of the research subjects in clinical research because it focuses on information that is *relevant to them* rather than the researcher;⁵⁸ hence, it helps in promoting the decisional autonomy of the participants.

Herein lies another difference between the legal doctrine and the ethical approach to informed consent. The ethical requirement of information disclosure is not just about how much or what is disclosed. It places significant importance on the comprehension of the information for the consent to be truly informed. However, assessing comprehension is not as easy or even as practicable as it may seem. Unless the researchers are willing to conduct tests or assessments on the information imparted to the subjects, there is hardly another way of knowing what the research subjects really understood. Nevertheless, as some teachers instinctively know that someone’s ability to regurgitate technical information does not equal the ability to truly understand that information, similarly a test conducted along those lines would not really prove a research subject’s comprehension of the study design.

It is also extensively believed that comprehension of information is much less in developing countries because of socio-economic factors, like illiteracy, cultural variations, lack of familiarity with biomedical procedures, and so on.⁵⁹ This is a

⁵⁷ *Id.*; see also V. Dranseika, et al., *Relevant Information and Informed Consent in Research: In Defense of the Subjective Standard of Disclosure*, SCIENCE AND ENGINEERING ETHICS, Vol. 23, Issue No. 1, (2017).

⁵⁸ *Id.* Dranseika, et al., (2017).

⁵⁹ M. Angell, *Investigators’ Responsibilities for Human Participants In Developing Countries*, NEW ENGLAND JOURNAL OF MEDICINE, Vol. 342, Issue No. 13, (2000), pp. 967-969; G. J. Annas & M. A. Grodin, *Human Rights and Maternal-Fetal HIV Transmission Prevention Trials in Africa*, AMERICAN JOURNAL OF PUBLIC HEALTH, Vol. 88, (1998), pp. 560-563; D. B. Resnick, *The Ethics of HIV Research in Developing Nations*, BIOETHICS, Vol. 12, (1998), pp. 286-306; D. J. Rothman, *The Shame of Medical Research*, NEW YORK REVIEW OF BOOKS, Vol. 47, Issue No. 19, (2000), pp. 60-64; S. LaFraniere, et al., *The Dilemma: Submit or Suffer ‘Uninformed Consent’ Is Rising Ethic of the Drug Test Boom*, THE WASHINGTON POST, (December 19, 2000), available at <http://www.washingtonpost.com/wp-dyn/content/article/2008/10/01/AR2008100101150.html> (last accessed on June 2, 2018); C. Levine, *Placebos and HIV: Lessons Learned*, HASTINGS CENTER REPORT, Vol. 28, (1998), pp. 43-48; D. J. Krogstad, et al., *Informed Consent in International Research: The Rationale for Different Approaches*, AMERICAN JOURNAL OF TROPICAL MEDICINE AND HYGIENE, Vol. 83, (2010), pp. 743-747; M. T. White, *Guidelines for IRB Review of International Collaborative Medical Research: A Proposal*, JOURNAL OF LAW AND MEDICAL ETHICS, Vol. 27, (1999), pp. 87-94.

widely popular generalisation pertaining to developing countries. However, studies conducted to empirically assess comprehension of information in clinical trials across developed and developing countries have shown similar problems with informed consent procedures in different settings.⁶⁰ In fact, recent studies comparing the levels of comprehension between participants in developed and developing countries have found a similar *quality* of informed consent in both developing and developed countries.⁶¹ These studies show that most ethical issues involving informed consent in research, including comprehension of information, correspond more or less equally to both developing and developed countries.

It is important to note that *assessing* comprehension of information is not a legal requirement for valid informed consent.⁶² However, ensuring that the

⁶⁰ The common problems with informed consent procedures, involving one-meeting consent process as opposed to multiple meetings with counsellors and investigators, include low retention of information by the participants, lack of detailed knowledge about procedures, and no clarity upon right to withdraw from participation. The comprehension test results were significantly improved with repeated consent counselling sessions in both developed and developing countries. *See for example* N. Lynoe, et al., *Informed consent: Study of quality of information given to participants in a clinical trial*, THE BRITISH MEDICAL JOURNAL, Vol. 303, (1991), pp. 610–613; L. H. Chaisson, et al., *Repeated Assessments of Informed Consent Comprehension among HIV-Infected Participants of a Three-Year Clinical Trial in Botswana*, PLOS ONE, Vol. 6, Issue No. 10, (2011); D. W. Fitzgerald, *Comprehension during informed consent in a less-developed country*, THE LANCET, Vol. 360, Issue No. 9342, (2002), pp. 1301–1302.

⁶¹ A. Mandava, et al., *The quality of informed consent: mapping the landscape. A review of empirical data from developing and developed countries*, JOURNAL OF MEDICAL ETHICS, Vol. 38, Issue No. 6, (2012), this study showed that assertions claiming informed consent being worse in developing countries was a simplification of a complex picture. It compared 47 studies done on comprehension in informed consent procedures conducted between 1966-2010 and showed that while participants in developing countries were less likely to refuse or withdraw from trial studies for being more worried about the consequences of such refusal, general comprehension of study information varied among participants in both developed and developing countries. For instance, comprehension of randomisation and placebo controlled designs was poorer in both as compared to other aspects of trials. *See also* D. J. Diermert, et al., *A Comparison of the Quality of Informed Consent for Clinical Trials of an Experimental Hookworm Vaccine Conducted in Developed and Developing Countries*, PLOS NEGLECTED TROPICAL DISEASE, Vol. 11, Issue No. 1, (January 2017), this study was conducted in Brazil and United States and showed variations on different variables between participants in both the countries, but overall comprehension quality was deemed to be more or less similar.

⁶² This comes with a caveat, while ‘assessing comprehension’ is not *per se* a legal requirement for valid informed consent; the physicians have the duty to take reasonable steps to ascertain that the patients understand the message being conveyed. This has been made clear by judges in UK and Canada, *see* *Montgomery v. Lanarkshire Health Board* (Scotland), [2015] UKSC 11, ¶ 90; *Ciarlariello v. Schacter*, (1993) 2 SCR 119 *cf* *Byciuk v. Hollingsworth*, 2004 ABQB 370; *Al Hamwi v Johnston* [2005] Lloyd’s Rep Med 309.

participant also understands the information conveyed is an important ethical requirement.⁶³ Some argue that it is an ethical aspiration and should not be confused with a minimum ethical standard, and that research with a low level of risk does not require a high level of comprehension.⁶⁴ Some argue that a lot more information ought to be disclosed than what can be easily understood in order to have valid consent.⁶⁵ This essentially means that information disclosure has to be full and complete, irrespective of the percentage of information comprehended by the research subject.

Comprehension of information marks the difference between what some scholars call ‘understood consent’ versus ‘informed consent’.⁶⁶ The former is a growing sub-field with scholars searching for innovative solutions, like the use of multimedia to help participants understand the information better.⁶⁷ Numerous studies have already been conducted to suggest methods to maximise comprehension in clinical research.⁶⁸ However, these studies are geared towards improving the process of imparting information rather than figuring out methods that best assess

⁶³ CIOMS Ethical Guidelines, *supra* note 12.

⁶⁴ G. Sreenivasan, *Does informed consent to research require comprehension?*, THE LANCET, Vol. 362, (December 2003); T. Walker, *Informed consent and the requirement to ensure understanding*, JOURNAL OF APPLIED PHILOSOPHY, Vol. 29, (2011), pp. 50–62.

⁶⁵ *Id.* Walker (2011).

⁶⁶ Z. A. Bhutta, *Beyond informed Consent*, BULLETIN OF THE WORLD HEALTH ORGANISATION, Vol. 82, (2004), pp. 771-777

⁶⁷ M. O. Afolabi, et al., *Multimedia Informed Consent Tool for a Low Literacy African Research Population: Development and Pilot-Testing*, JOURNAL OF CLINICAL RESEARCH AND BIOETHICS, Vol. 5, Issue no. 3, (2014).

⁶⁸ Most studies have suggested decreasing the length and complexity of the informed consent form for greater comprehension and satisfaction with the informed consent process. *See for example* J. Flory & E. Emanuel, *Interventions to improve research participants' understanding in informed consent for research: A systematic review*, JOURNAL OF AMERICAN MEDICAL ASSOCIATION, Vol. 292, (2004), pp. 1593–1601; E. Bjorn, et al., *Can the written information to research subjects be improved?—an empirical study*, JOURNAL OF MEDICAL ETHICS, Vol. 25, (1999), pp. 263–267; D. R. Young, et al., *Informed consent documents: Increasing comprehension by reducing reading level*, IRB: ETHICS & HUMAN RESEARCH, Vol. 12, (1990), pp. 1–5; C. G. Rogers, et al., *Conventional consent with opting in versus simplified consent with opting out: An exploratory trial for studies that do not increase patient risk*, JOURNAL OF PEDIATRICS, Vol. 132, (1998), pp. 606–611; G. M. Dresden & M. A. Levitt, *Modifying a standard industry clinical trial consent form improves patient information retention as part of the informed consent process*, ACADEMIC EMERGENCY MEDICINE, Vol. 8, (2001), pp. 246–252; L. C. Epstein & L. Lasagna, *Obtaining informed consent: Form or substance*, ARCHIVES OF INTERNAL MEDICINE, Vol. 123, (1969), pp. 682–688;

comprehension, thereby confirming that assessing comprehension is not as straightforward as it may seem.

No matter what the level of comprehension, whether assessed during the informed consent process or not, assuring that the participant has enough information to be able to reasonably assess the risks and benefits to her person before consenting is an essential requirement of valid informed consent. This capacity to reasonably assess risks and benefits of research is the third requirement and will be discussed in the next section.

c) Capacity/Competence

A person's capacity to consent is often defined in relation to the information or knowledge that he or she has about the intended treatment or intervention. Simply put, a person is deemed *competent* to consent if she is able to understand what she is consenting to. The decision-making ability is sometimes referred to as 'competence' because what is at issue is 'the ability to perform a task'.⁶⁹ At other times, it is referred to as 'capacity' because the task in question involves the capacity to make a decision.⁷⁰ I will be using the term interchangeably even though I am aware that "capacity [usually] denotes a clinical status as judged by a health care professional whereas competence denotes a legal status as judged by a legal professional, i.e., a judge."⁷¹

Appelbaum and Grisso analysed the legal assessment of patient's capacities to consent to treatment,⁷² and found that most features of competence could be categorised as follows:

- i) The ability to communicate choices
- ii) The ability to understand information

⁶⁹ T. L. BEAUCHAMP & J. F. CHILDRESS, *PRINCIPLES OF BIOMEDICAL ETHICS*, (5th edn., Oxford University Press, 2001), p. 70

⁷⁰ A. E. BUCHANAN & D. W. BROCK, *DECIDING FOR OTHERS: THE ETHICS OF SURROGATE DECISION MAKING*, (Cambridge University Press, 1989), p. 84.

⁷¹ D. C. Marson, *Loss of competency in Alzheimer's disease: Conceptual and psychometric approaches*, *INTERNATIONAL JOURNAL OF LAW AND PSYCHIATRY*, 24, (2001), pp. 267 – 283.

⁷² P. S. Appelbaum & T. Grisso, *Assessing Patients' Capacities to Consent to Treatment*, *THE NEW ENGLAND JOURNAL OF MEDICINE*, Vol. 319, (1988), pp. 1635-1638.

- iii) Appreciating the situation and its consequences
- iv) Rational manipulation of information.

In bioethical and philosophical literature, each of these categories have elucidations and theories of their own, especially the concept of rationality.⁷³ Tackling these concepts individually would be beyond the scope of this thesis. For now, we will assume a layperson's understanding of these categories. Nevertheless, it would help our empirical analysis later to note the difference between categories ii) and iii), which is the ability to understand information and the ability to appreciate the situation and its consequences. Sometimes a person can understand what she is told without fully understanding the implications that it carries for one's future. The ability to appreciate the circumstances and their consequences is an important measure for determining the capacity to consent. In the clinical research context, the ability to appreciate the risks and benefits of research is a defining feature of competence.⁷⁴ The level of capacity required for legal competence rises with the extent to which the risks outweigh the benefits. The same rule applies in the treatment context, as Lord Donaldson wrote:

What matters is that the doctors should consider whether at that time he had a capacity which was commensurate with the gravity of the decision. The more serious the decision, the greater the capacity required.⁷⁵

In law, a person is presumed to have capacity unless it is established that the person lacks capacity.⁷⁶ Physicians, psychiatrists, and other scholars have developed numerous capacity assessment tools and standards in the past years.⁷⁷ Appelbaum

⁷³ If we were to take Amartya Sen's definition, he defines rationality as the "discipline of subjecting one's choices – of actions as well as objectives, values, and priorities – to reasoned scrutiny", see A. SEN, *RATIONALITY AND FREEDOM* (Harvard University Press, 2004), p. 4. Freedman says that rational manipulation of information involves the ability to reach conclusions that are logically consistent with the starting premises, see B. Freedman, *Competence, marginal and otherwise: concepts and ethics*, *INTERNATIONAL JOURNAL OF LAW AND PSYCHIATRY*, Vol. 4, (1981), pp. 53–72

⁷⁴ American Psychiatric Association, *Guidelines for assessing the decision-making capacities of potential research subjects with cognitive impairment*, *AMERICAN JOURNAL OF PSYCHIATRY*, Vol. 155, Issue No. 11, (1998), pp. 1649-1650.

⁷⁵ *Re T (adult: refusal to consent to treatment)* [1992] 4 All E.R. 649.

⁷⁶ See for example, Mental Capacity Act (UK), 2005, Section 1(2).

⁷⁷ An overview of the different assessment tools developed for assessing competency in treatment and research contexts, including, but not limited to, the Hopkins Competency Assessment Test (HCAT),

and Roth suggest that when a court or a clinician makes an assessment, the standards that are eventually chosen to assess capacity are the product of competing societal values and the goals of the researchers.⁷⁸ For example, if encouragement of autonomy is the goal, the standard for capacity will be relatively lax. However, if the ethical imperative of beneficence and non-maleficence⁷⁹ were to be achieved, then capacity assessment would require a strict set of standards, such as rationality or appreciation of emotions and values.⁸⁰ Here lies a major difference between the theory and practice of informed consent: while the courts might consider assessment standards based on the different goals of informed consent, the participant recruiters for human subject research barely employ such standards. There is little evidence suggesting that trials carried out across the world employ capacity assessments for all research studies and not just for studies on incapacitated individuals. My research findings, discussed in Chapter 6, will show that if a study has nothing to do with minor children or people of unsound mind, a recruiter's usual test for capacity to consent is the legal age of majority.

Part 1 looked at the essentials of informed consent and the conceptual debates that surround them. It gave a brief overview of how law and ethics approach the fundamentals of consent differently. Part 2 will show how the essential features of informed consent look like withi the clinical research context of India.

MacArthur Treatment Competence Study (MTCS), MacArthur Competence Assessment Tool—Treatment (MacCAT-T), The Mini Mental Status Examination (MMSE), etc., can be found in the following article. See E.D. Sturman, *The capacity to consent to treatment and research: A review of standardized assessment tools*, Clinical Psychology Review, Vol. 25, (2005), pp. 954 – 974.

⁷⁸ P. S. Appelbaum, & L. H. Roth, *Competency to consent to research. A psychiatric overview*, ARCHIVES OF GENERAL PSYCHIATRY, Vol. 39, (1982), pp. 951 – 958, p. 956.

⁷⁹ Of the four major principles of biomedical ethics (beneficence, non-maleficence, justice, and autonomy), 'beneficence' means to do good by balancing the benefits of research against the risks involved, 'non-maleficence' means to avoid unnecessary harm to the participant. The four principles were introduced by Beauchamp & Childress in their seminal work, 'Principles of Biomedical Ethics', *supra* note 69.

⁸⁰ Appelbaum, & Roth (1982), *supra* note 78.

Part 2. Informed consent in India

Ethical codes of conduct in medicine and research were not new to India. Before Europeans brought modern medicine to India, India had its own ancient tradition of medicine. The corpus of Hindu literature pertaining to health and medicine is called *Ayurveda* (knowledge of long life).⁸¹ The texts of *Ayurveda*, particularly *Charaka Samhitā* (written between the fourth century BCE and the second century CE),⁸² were the reference texts for medical morality and conduct in treatment as well as in research.⁸³ *Charaka* advises physicians to take into confidence the relatives of the patients, the elders in the community, and the state officials before performing interventions that could result in the patient's death.⁸⁴ *Arthashastra*, a treatise on statecraft from around the third century BC, suggested capital punishment for physicians who did not obtain the prior permission of the state before performing a life-threatening surgery.⁸⁵ However, patients' preferences for decision-making regarding their own treatment are not mentioned in the ancient texts.⁸⁶ In the centuries preceding European colonialism, many different medical traditions were practiced in India and each prescribed their own codes of conduct for physicians and

⁸¹ P. N. Desai, *Medical Ethics in India*, THE JOURNAL OF MEDICINE AND PHILOSOPHY, Vol. 13, (1988), 231-255; See generally DAGMAR WUJASTYK, WELL-MANNERED MEDICINE: MEDICAL ETHICS AND ETIQUETTE IN CLASSICAL AYURVEDA (Oxford University Press, 2012).

⁸² The exact date of the composition of this text is unknown, but it falls within this timeline according to historians, see G. J. Meulenbeld, *Caraka, his identity and date*, in: A HISTORY OF INDIAN MEDICAL LITERATURE, (Groningen: 1999).

⁸³ Desai (1988), *supra* note 81. Moreover, the concept of *Dharma*, which has different meanings in Hinduism, Buddhism, Jainism and Sikhism, has been a constant in governing morality in India since ancient times. It could mean, inter alia, duty, morality, virtue, religion, or the power which upholds the society and, in turn, the Universe. See D. R. Davis (Jr.), *An Indian Philosophy of Law: Vijñāneśvara's Epitome of the Law*, in: J. GANERI (ED), THE OXFORD HANDBOOK OF INDIAN PHILOSOPHY, (2015).

⁸⁴ C. M. Francis, *Medical ethics in India: ancient and modern (I)*, INDIAN JOURNAL OF MEDICAL ETHICS, Vol. 4, Issue No. 4, (1996).

⁸⁵ "Physicians undertaking medical treatment without intimating (to the government) the dangerous nature of the disease shall, if the patient dies, be punished with the first amercement. If the death of a patient under treatment is due to carelessness in the treatment, the physician shall be punished with the middle-most amercement. Growth of disease due to negligence or indifference (karmavadha) of a physician shall be regarded as assault or violence." See KAUTILYA'S ARTHASHASTRA: BOOK IV, THE REMOVAL OF THORNS, as translated from Sanskrit by R. Shamasastri, (Bangalore: Government Press, 1915), pp.253-296. See also M. S. Valiathan, *Bioethics and Ayurveda*, INDIAN JOURNAL OF MEDICAL ETHICS, Vol. 5, Issue no. 1, (2008).

⁸⁶ N. Kumar, *Informed Consent; Past and Present*, PERSPECTIVES IN CLINICAL RESEARCH, Vol. 4, Issue No. 1, (2013) pp. 21-25.

surgeons.⁸⁷ European colonialism brought with itself modern medicine and a new legal system that intermixed with the existing systems.

The modern medical research history in India dates back to the first meeting of the Indian Research Fund Association (IRFA) in 1911. This association initiated several projects between 1918-1920 to find indigenous cures for diseases like malaria, beriberi, and kala azar.⁸⁸ The first Clinical Research Unit (CRU) in India was established at the Indian Cancer Research Centre in Bombay in 1945.⁸⁹ The IRFA was re-designated as the Indian Council of Medical Research (ICMR) in 1949 and it became the apex body for the formulation, coordination, and promotion of biomedical research. Over the past seven decades, the ICMR has established many national research centres in the fields of nutrition, genetics, AIDS, tuberculosis, toxicology, cancer, traditional medicine, leprosy, viral diseases, enteric diseases, cholera, reproductive disorders, gas disaster, genetics, and so on. ICMR is an arm of the government that co-ordinates (not-for-profit) research into diseases that encompass the public health needs of the nation. Privatisation in treatment and research in India started around the 1980s and became stronger after the liberalisation of the Indian economy in 1991.⁹⁰ With the onset of globalisation, the private sector mostly focused on innovation and profit rather than on unmet health needs of populations⁹¹ (discounting instances of public-private partnership models in research where a pharmaceutical corporation is involved in a not-for-profit capacity). This meant that regulation of clinical research needed to be different to encompass private actors.

⁸⁷ Other medical traditions like Unani, Siddhi, Homeopathy and Indigenous, were also practiced in India and had their respective codes of conduct. See B. Ravishankar & V. J. Shukla, *Indian Systems of Medicine: A Brief Profile*, AFRICAN JOURNAL OF TRADITIONAL, COMPLEMENTARY AND ALTERNATIVE MEDICINES, Vol. 4, Issue No. 3, (2007).

⁸⁸ A. Bhatt, *Evolution of Clinical Research: A History Before and Beyond James Lind*, PERSPECTIVES IN CLINICAL RESEARCH, Vol. 1, Issue No. 1, (2010).

⁸⁹ *Id.*

⁹⁰ V. R. Baru, *Public Sector Doctors in an Era of Commercialisation*, in: K. SHEIKH & A. GEORGE (EDS), *HEALTH PROVIDERS IN INDIA: ON THE FRONTLINES OF CHANGE*, (Routledge, 2010), pp. 81-89.

⁹¹ J. Chataway, et al., *Frameworks for Pharmaceutical Innovation in Developing Countries—The Case of Indian Pharma*, TECHNOLOGY ANALYSIS & STRATEGIC MANAGEMENT, Vol. 19, Issue No. 5, (2007), pp. 697-708.

Human subject research regulation in India, particularly regulation of informed consent procedures, is a recent occurrence. The ICMR released a Policy Statement on Ethical Considerations Involved in Research on Human Subjects in the year 1980. This policy statement acted as a predecessor for ethical guidelines governing human subject research in India and made informed consent mandatory for research conducted on human subjects.⁹² Following this, the Central Drugs Standard Control Organization (CDSCO), which is the central regulatory authority for discharging functions assigned to the central government under the Drugs and Cosmetics Act, 1940, introduced certain provisions on the conduct of clinical trials.

The year 1988 saw the introduction of requirements and guidelines on clinical trials for import and manufacture of new drugs as Schedule Y in the Drugs and Cosmetics Rules of 1945.⁹³ The first Central Ethics Committee (CEC) was established in 1996 to look into ethical matters pertaining to medical and health research and the ethical guidelines for human subject research were first released by the ICMR in 2000, which were updated in 2006 and 2017.⁹⁴ India adopted the Good Clinical Practice (GCP) guidelines (originally released by the ICH) in 2001; these guidelines prescribe the ethical and scientific quality standards for designing, conducting, and recording trials that involve the participation of human subjects.⁹⁵ The GCP guidelines lay down an elaborate consent process that is expected to be followed by researchers.⁹⁶

Despite being the primary sources for governing the ethics of clinical research in India, the ICMR and GCP guidelines lack enforceability. Schedule Y is the lone legal source that makes informed consent mandatory for clinical research in India. As noted in the previous chapter, it was amended in 2005⁹⁷ to eliminate earlier limitations and to encourage clinical trials while also protecting the rights of the trial

⁹² U. M. Thatte & P. A. Marathe, *Ethics Committees in India: Past, present and future*, PERSPECTIVES IN CLINICAL RESEARCH, Vol. 8, Issue No. 1, (2017), pp. 22-30.

⁹³ Through General Statutory Rule (GSR) 944(E) dated 21.09.1988 subsequently corrected by GSR 588 (E) dated 02.06.1989.

⁹⁴ ICMR Ethical Guidelines 2017, *supra* note 15.

⁹⁵ Central Drugs Standard Control Organization (CDSCO), Good Clinical Practice Guidelines (GCP guidelines), available at <http://www.cdscsco.nic.in/html/GCP1.html> (last accessed June 29, 2018)

⁹⁶ *Id.* Section 2.4.3. on Informed Consent Process.

⁹⁷ Vide GSR 32 (E) dated 20.01.2005.

subjects. Where the amended schedule outlines the process for informed consent and the responsibilities of the investigators, such clarity was lacking when the schedule was first introduced in 1988. Pursuant to the SAM case (filed in 2012), this schedule was further amended between 2013-2015 to bring in newer rules pertaining to compensating trial participants in case of injury and death from trial participation and for making audio-video recording of informed consent mandatory for vulnerable trial participants.⁹⁸ As evident, informed consent has been the subject of multiple regulatory interventions since the 1980s. However, the ground realities are often slow to reflect regulatory changes. In the next few sections, the focus will be on how the informed consent process has advanced over time on the ground.

3.2. The face of informed consent in India

In a 2016 survey that aimed to assess the quality of ethics of clinical research processes the surveyors found that even if the average informed consent document used in research was to be designed as per the regulatory requirements, it was unlikely to produce the level of “informed consent as ethically required”.⁹⁹ Let us examine this further by looking at the three essentials as discussed in Part 1.

In a study conducted by DeCosta and colleagues on community-based trials in rural north India the authors found:

An important finding of our study was that the majority of the community interviewed could decide about participation only after discussing it with other community members. Only about a third of all

⁹⁸ The audio-video recording mandate came through Ministry of Health and Family Welfare, Gazette Notification G.S.R. 611/(E), (July 31, 2015), available at <http://www.ferci.org/wp-content/uploads/2014/07/Gazette-Notification-31-July-2015-AV-consent.pdf> (last accessed on July 2, 2018). Furthermore, as was noted in the last chapter, the 1945 Rules and the amendment do not define vulnerability. As a reference point, the ICMR guidelines released in 2017 define vulnerable as those that are “socially, economically or politically disadvantaged and therefore susceptible to being exploited; incapable of making a voluntary informed decision for themselves or whose autonomy is compromised temporarily or permanently, for example people who are unconscious, differently abled; able to give consent, but whose voluntariness or understanding is compromised due to their situational conditions; or unduly influenced either by the expectation of benefits or fear of retaliation in case of refusal to participate which may lead them to give consent.” See ICMR Ethical Guidelines, 2017, *supra* note 15.

⁹⁹ M. Patel, et al., *Informed Consent Document and Process in India: Ethical and Quality Issues*, ASIAN BIOETHICS REVIEW, Vol. 8, Issue No. 1, (2016), pp. 37-52,

respondents could take an exclusively independent, non-consultative decision. In the case of the few women interviewed, this proportion was even lower - most believed they would be unable to decide for themselves.¹⁰⁰

Such findings, where people's decisions regarding trial participation are not entirely their own, have been repeated in other empirical studies from India.¹⁰¹ This provides a challenge to the conceptual understanding of voluntariness as "free and unrestrained will" as outlined in Part 1 above. In a 2010 survey conducted on investigator perceptions regarding research ethics in clinical trials in India, only 18% of the surveyed investigators believed that their participants were "truly autonomous" agents with no controlling influences affecting their decisions and voluntariness.¹⁰²

Yet the primary problem with the informed consent processes in India appears to be the inadequacy of information disclosure. Most empirical studies conducted in this area suggest that participants are either not fully informed¹⁰³ of important particulars about the study or they do not understand the information adequately.¹⁰⁴ This is additionally problematic when researchers adopt a paternalistic

¹⁰⁰ A. DeCosta, et al., *Community based trials and informed consent in rural north India*, JOURNAL OF MEDICAL ETHICS, Vol. 30, (2004), pp. 318-323. In this study 57 households in village called Chainsa in rural north India were interviewed around a hypothetical scenario in which a community based clinical investigation was planned to take place in the village. The interviewees were informed that the intervention could include either a simple interview, giving a blood sample, having a vaccine, or taking a new drug. Then researchers asked some questions about their willingness to participate, about decision-makers in the family, etc.

¹⁰¹ S. Nadimpally & D. Bhagianadh, *"The invisible": Participant's experiences in clinical trials*, PERSPECTIVES IN CLINICAL RESEARCH, Vol. 8, Issue No. 1, (2017); S. Sahay, et al., *Experiences in recruiting volunteers through community based initiatives in Phase-I vaccine trials in India*, HUMAN VACCINES & IMMUNOTHERAPEUTICS, Vol. 10, Issue no. 2, (2014).

¹⁰² S. Batra & P. Kochhar, *Survey on Perceptions of Indian Investigators on Research Ethics*, PERSPECTIVES IN CLINICAL RESEARCH, Vol. 1, Issue no. 3, (2010).

¹⁰³ DeCosta, et al, (2004), *supra* note 98; Patel, et al, (2016), *supra* note 97; S. Kumar, et al., *How 'informed' is informed consent? Findings from a study in South India*, INDIAN JOURNAL OF MEDICAL ETHICS, Vol. 9, Issue No. 3, (2012); M. Vaz & K. Srinivasan, *Listening to the voices of the general public in India on biomedical research--an exploratory study*, INDIAN JOURNAL OF MEDICAL ETHICS, Vol. 12, Issue No. 2, (2015).

¹⁰⁴ N. S. Joglekar, et al., *Correlates of lower comprehension of informed consent among participants enrolled in a cohort study in Pune, India*, INTERNATIONAL HEALTH, Vol. 5, Issue No. 1, (2013), pp. 64-71; R. Sarkar, et al., *Comparison of group counseling with individual counseling in the comprehension of informed consent: a randomized controlled trial*, BMC MEDICAL ETHICS, Vol. 8,

attitude towards their participants, as was revealed in a study conducted on informed consent in genetic research and biobanking studies on participants in rural India. One doctor/investigator from the study is quoted as saying:

What's the use of informed consent when many are suffering and dying of diseases? We need to screen them to know their status and take appropriate action for treatment or counselling to ensure that the disease burden is reduced in the society. A mere informed consent will only add to their misery. Do the people who prepared ethical guidelines understand the situation at grass-roots level? (Dr D., project director of a sickle cell interventional project in the state of Chhatisgarh)¹⁰⁵

Researchers have found standard informed consent procedures to be deficient in terms of allowing participants to comprehend the nature, design, and risks and benefits of the study.¹⁰⁶ This is particularly the case for participants with low or no formal education. Moreover, despite there being India-specific research suggesting methods, like the use of culturally appropriate visual aid tools, which could be used to improve comprehension of participants with low education,¹⁰⁷ such tools are not widely employed.¹⁰⁸

As for the essential requirement of capacity to consent, India lacks a statute akin to the Mental Capacity Act, (MCA) 2005 in the UK. This means that there is no separate legislation outlining codes of practice through which mental capacity can be assessed such as the two-stage test laid out by the MCA.¹⁰⁹ The Indian legislature

Issue No. 8. (2010); S. Bhansali, et al., *Evaluation of the ability of clinical research participants to comprehend informed consent form*, CONTEMPORARY CLINICAL TRIALS, Vol. 30, Issue No. 5, (2009).

¹⁰⁵ P. K. Patra & M. Sleeboom-Faulkner, *Informed consent in genetic research and biobanking in India: some common impediments*, GENOMICS, SOCIETY, AND POLICY, Vol. 5, Issue No. 1, (2009)

¹⁰⁶ See *supra* notes 101 & 102.

¹⁰⁷ J. Sastry, et al., *Optimizing the HIV/AIDS informed consent process in India*, BMC MEDICINE, Vol. 2, Issue no. 28, (2004).

¹⁰⁸ This general finding stems from my empirical research and is corroborated by other researchers who have written on informed consent procedures in India. See further Chapters 6 & 7 of the thesis.

¹⁰⁹ According to the Codes of Practice released by Lord Chancellor in 2007 under Sections 42 and 43 of the UK Mental Capacity Act, 2005, there is a two-stage test to assess the capacity of the person: "Stage 1: Does the person have an impairment of, or a disturbance in the functioning of, their mind or brain? Stage 2: Does the impairment or disturbance mean that the person is unable to make a specific decision when they need to?" See, Mental Capacity Act, 2005, Code of Practice, available at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/497253/Mental-capacity-act-code-of-practice.pdf (last accessed July 2, 2018)

recently passed the Mental Health Care Act, 2017 (MHCA) that acknowledged that capacity for decision-making in treatment was to be presumed unless it was otherwise established that such capacity was lacking.¹¹⁰ However, provisions for the assessment of capacity remain unclear in the MHCA¹¹¹ and are also absent from the ethical guidelines that govern human subject research.¹¹² Furthermore, capacity is not just restricted to sanity or mental health. According to the ethical approach to informed consent, it includes the ability to make sound decisions and the ability to weigh the consequences of such decisions.¹¹³ Age is an indicator of having reached such capacity, and therefore, people of minor years need a legally authorised representative (LAR) to authorise research participation on their behalf. However, there have been instances where the LAR for a participant was not the appropriate representative or was not capable of understanding the information pertaining to the study.¹¹⁴ There have also been instances where research has been carried out on mentally incapacitated participants without adequate informed consent of the participants.¹¹⁵

The general situation is such that many researchers have raised concerns over the dubious nature of informed consent procedures in research studies conducted in different parts of India.¹¹⁶ A few such ethically dubious studies led to the filing of the SAM case that brought to the fore the ethical violations and regulatory loopholes in

¹¹⁰ The Mental Health Care Act, 2017 (Government of India, Act No. 10 of 2017).

¹¹¹ R. M. Duffy & B. D. Kelly, *Concordance of the Indian Mental Healthcare Act 2017 with the World Health Organization's Checklist on Mental Health Legislation*, INTERNATIONAL JOURNAL OF MENTAL HEALTH SYSTEMS, Vol. 11, (2017).

¹¹² ICMR Ethical Guidelines, 2017, *supra* note 15.

¹¹³ See Part 1, section 2.3.1. (c) above.

¹¹⁴ *Infra* note 131. See HPV vaccine case in section 2.2.1. (3) below.

¹¹⁵ N. Dixit, *Indore psychiatrists admit to conducting drug trials on mentally ill patients*, INDIA TODAY, (January, 23, 2012), available at <https://www.indiatoday.in/india/north/story/indore-psychiatrists-admit-to-conducting-drug-trials-on-mentally-ill-patients-90671-2012-01-23> (last accessed on July 3, 2018); see also S. Kharawala & J. Dalal, *Challenges in conducting psychiatry studies in India*, PERSPECTIVES IN CLINICAL RESEARCH, Vol. 2, Issue No. 1, (2011).

¹¹⁶ W. A. Cook, *Questionable informed consent of vulnerable pregnant research participants in South India –What a staff reminder poster does not say*, NURSING ETHICS, Vol. 22, Issue No. 2, (2015), 264-272; M. Yadav, et al., *Role of Informed Consent in India Past, Present and Future Trends*, JOURNAL OF INDIAN ACADEMY OF FORENSIC MEDICINE, Vol. 36, Issue no. 4, (2014); S. Ramanathan, *Decolonising Mental Health: How India's Mentally Ill Are Being Drugged Without Consent*, THE NEWS MINUTE, (August 31, 2017) available at <https://bit.ly/2MijHsO> (last accessed on July 2, 2018)

clinical research and led the government to strengthen regulations pertaining to informed consent. I will outline a few of these in the next section.

3.2.1. Specific instances of dubious informed consent procedures

The SAM case changed the narrative of clinical research ethics and regulation in India. This case led to further amendments (between 2013-2015) in Schedule Y pertaining to the rights of the trial participants.¹¹⁷ The SAM case's original petition, (a copy of which I procured from the Supreme Court Registry in India, relevant portions highlighted in Appendix I) gives examples of numerous unethically conducted trials conducted in India. These specific cases highlight how informed consent norms can be, and have been, violated in rural/semi-urban resource-poor settings. I will outline three pertinent cases hereunder:

1) Unethical Trials in Indore: The petitioners of the SAM case submitted a report of the Economic Offences Wing (EOW) dated 24.06.2011, where a complaint was filed by Dr. Anand Singh Raje, against unsupervised clinical trials conducted in M.Y. Hospital of M.G.M. Medical College. Allegations were made against six doctors of the hospital that they had received *Crores* of Indian Rupees¹¹⁸ from multinational drug companies. The complaint also alleged that the government doctors were conducting private trials while holding their official positions and without obtaining consent from the administration, and that they were “committing fraud” on the patients and their relatives. An investigation was conducted into the complaint. The investigative inquiry found that the Principal Investigators (PIs) were members or Secretaries of the Ethics Committees (ECs) and that these ECs rarely followed standard procedures. It was found that the Contract Research Organisations (CROs), PIs, and ECs regularly violated ethical guidelines and that the core principle relating to obtaining voluntary informed consent from the participants was completely disregarded. They found that the PI contravened Section 20 A of the Medical Council Act, 1956,¹¹⁹ and committed professional misconduct. They also found that

¹¹⁷ *Supra* note 98.

¹¹⁸ 1 Crore denotes a unit of 10 million. 1 Crore INR would be 147,000 USD approximately.

¹¹⁹ Section 20A of the Indian Medical Council Act, 1956, says that the Medical Council of India may prescribe standards of professional conduct and etiquette and a code of ethics for medical practitioners. It also lays down that the regulations made by the Council “may specify which

there was no transparency in the trial process. The trial participants were denied their entitlements and financial safeguards, like insurance, in instances of Serious and Adverse Events (SAEs).

Despite the verification of the complaint, a sufficient basis was not found to initiate criminal proceedings against the doctors who were in the employment of the government. However, the EOW made certain recommendations asking the government to take appropriate action against the doctors for violating the ICMR Guidelines, specifically for violating the principle of informed consent. The report urged the government to take disciplinary action against the doctors under the Code of Medical Ethics Regulation of 2002 (amended in 2009) and to ask the doctors to deposit 10% of the money received from the trials in the Medical Education Department of M.G.M. Medical College, Indore.¹²⁰

Media reports suggested that departmental action was taken against twelve doctors and they were asked to pay fines for violation of the ethical guidelines.¹²¹ However, in a reply to the Lancet's report on this case, the doctors involved in this trial stressed that the trials that they were involved in were legal and ethically done as per the ICMR Guidelines.¹²² They decried the "partisan coverage" of this case and said the fines imposed on the doctors were for a "trivial technicality of failing to provide information to (another part of) the health department about some details of the clinical trials." They stressed that the fines had "nothing do with the legality, ethics, or proper conduct of the trials as per norms of good clinical practice."¹²³

violations thereof shall constitute infamous conduct in any professional respect, that is to say, professional misconduct, and such provision shall have effect notwithstanding anything contained in any law for the time being in force."

¹²⁰ W.P. (Civil) 33/2012, Supreme Court of India (hereafter SAM PIL), ¶ 33-39, p. 54-64.

¹²¹ V. Krishnan, *MP govt to act against 11 Indore doctors*, LIVE MINT, (October 22, 2012), available at <http://www.livemint.com/Politics/Nxm wzRufEq2Efjcl888OFJ/MP-govt-to-act-against-11-Indore-doctors.html> (last accessed on June 2, 2018)

¹²² ICMR Ethical Guidelines *supra* note 15.

¹²³ A. Pauranik, et al, (Doctors at MGM College, Indore), *Misleading report on clinical trials in India*, THE LANCET (Correspondence Section), Vol 379, (May 26, 2012), available at [http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736\(12\)60849-6.pdf](http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(12)60849-6.pdf) (last accessed on June 2, 2018)

The next example, also cited in the SAM PIL, highlights the issue of conducting trials on patients with reduced autonomy and is also from a city in Madhya Pradesh, which is the state where the petitioner NGO is based.

2) Trials on the Bhopal Gas Victims in Bhopal: The petitioners submitted records of trials conducted on Bhopal Gas Tragedy victims in Bhopal. The petitioners claimed that in these trials most of the patients could barely form a signature and had no understanding of the particulars of the informed consent form.¹²⁴ The Bhopal Memorial Hospital and Research Centre (BMHRC) was built to help victims of the Bhopal Gas Disaster that occurred in 1984.¹²⁵ Between the years 2004-2008, over 160 patients in this hospital were subjected to trials of study drugs including New Chemical Entities (NCEs).¹²⁶ The petitioners claimed that the trials were unethical because a trial cannot be ethically conducted on people with reduced autonomy and the patients at BMHRC had “zero autonomy” since they were completely dependent on the treatment provided by the hospital.

The petitioners submitted a CD of the Al Jazeera documentary ‘Faultline: Outsourced Clinical Trials Overseas’ as supplementary evidence of the unethical trials conducted at BMHRC.¹²⁷ The petitioners claimed that in the three inspections done by the Drug Controller General of India (DCGI), it had been found that new drugs, like *Fondaparinux* and *Tigecycline*, and NCEs, like *Prasugrel* and *Telavancin*, were tested on patients, the majority of whom were disaster victims. However, the deaths that ensued were dismissed by the DCGI as “not related to the drug being tested”, without any independent verification. It must be noted that the exact details of this case study are hard to find from more authoritative sources, as the case was

¹²⁴ SAM PIL *supra* note 120, ¶44, p.71-73.

¹²⁵ See E. Broughton, *The Bhopal disaster and its aftermath: a review*, ENVIRONMENTAL HEALTH: A GLOBAL ACCESS SCIENCE SOURCE, Vol. 4, Issue No. 6, (2005).

¹²⁶ A New Chemical Entity (NCE) contains no active moiety that has been approved by the licensing authority in any other application submitted for approval under the relevant provisions of the Drugs and Cosmetics Act, 1940.

¹²⁷ [Video Documentary] Al Jazeera team, *Faultline: Outsourced Clinical Trial Overseas*, (July 2011), available at <https://www.aljazeera.com/programmes/faultlines/2011/07/2011711112453541600.html> (last accessed on June 29, 2018)

mostly reported in the news media.¹²⁸ Nonetheless, it is important because it shows how trial sponsors and investigators have been reported to have recruited disaster victims with compromised autonomy for trials.

The previous two cases from Madhya Pradesh do not have authoritative information on what transpired after allegations of violation of informed consent rules took place. However, the next case was a large-scale vaccination project that was reported to have flouted the informed consent procedures and a Parliamentary Committee was set up to look into the allegations. I will reproduce some findings from the inquiry report discussed below that demonstrate concerns about trialling on young girls below the age of majority.

3) The HPV vaccine (Gardasil and Cervarix) clinical trial (hereafter the HPV vaccine case):

The background to this case is set in the year 2009 when a vaccination project was launched in the states of Andhra Pradesh and Gujarat against Human Papilloma Virus (HPV), some types of which can cause cervical cancer. Girls between 10-14 years of age were given the vaccination. The project had two components - a Phase IV clinical trial of the HPV vaccination¹²⁹ and observational research on the delivery of the vaccine to establish if it would suit India's mass immunization program. The drugs had already been approved in the US and India. The project was designed and executed by PATH (Program for Appropriate Technology in Health), a US-based NGO, in collaboration with the Indian Council for Medical Research (ICMR), and the State Governments of Andhra Pradesh and Gujarat. The pharmaceutical company Merck developed and provided the vaccine *Gardasil* and GlaxoSmithKline developed and provided the vaccine *Cervarix*. The project was funded by the Bill and Melinda Gates Foundation. In April 2010, the Government of India suspended the program after health rights activists, women's rights groups, and some doctors

¹²⁸ N. Lakhani, *From tragedy to travesty: Drugs tested on survivors of Bhopal*, THE INDEPENDENT, (November 15, 2011), available at <http://www.independent.co.uk/news/world/asia/from-tragedy-to-travesty-drugs-tested-on-survivors-of-bhopal-6262412.html> (last accessed on June 2, 2018)

¹²⁹ Phase IV trials are done after a drug has proven efficacy and has been granted a licence, these are usually conducted after marketing approval to assess long term risks and benefits of the drug when used widely.

questioned its motivation, ethics, and informed consent procedures, especially after reports of the deaths of some of the vaccinated girls surfaced in the media. At the time of the suspension of the vaccination project, about 25,000 girls had already been vaccinated.¹³⁰

The Indian Government set up a Parliamentary Inquiry Committee to look into the “alleged irregularities in the conduct of studies using HPV vaccine” by PATH in India.¹³¹ The Committee concluded that the deaths of girls from amongst the trial participants were likely not related to the vaccine. But the committee found that the process of informed consent was inadequate. It described the process whereby school principals signed consent forms on behalf of the children as “wrongful authorization.” It found that:

...in Andhra Pradesh out of the 9543 forms, 1948 forms have thumb impressions while hostel wardens have signed 2763 forms. In Gujarat, out of the 6217 forms 3944 have thumb impressions and 5454 either signed or carried thumb impressions of guardians. The data also revealed that a very large number of parents/guardians are illiterate and could not even write in their local languages viz. Telugu or Gujarati...out of 100 consent forms for Andhra Pradesh project signatures of witnesses were missing in 69 forms. In many forms there were no dates. One particular person had signed seven forms. In fact the legality of Andhra Pradesh State Government directing headmasters in all private/Government/ashram/schools to sign the consent form on behalf of parents/guardians is highly questionable. The absence of photographs of parents/guardians/wardens on consent forms, the absence of signatures of investigators; the signatures of parents/guardians not matching with their names; the date of vaccination being much earlier than the date of signature of parents/guardian in the consent forms, etc. all speak of grave irregularities.¹³²

The report and recommendations of the Parliamentary Committee did not lead to any significant governmental action or sanction. This inaction on the part of the

¹³⁰ SAM PIL *supra* note 120, ¶ 45, p. 73-77.

¹³¹ Parliament Standing Committee, Rajya Sabha Report No. 72 on Health and Family Welfare, Seventy Second Report on Alleged Irregularities in the Conduct of Studies using Human Papilloma Virus (HPV) Vaccine by Path in India, (Department of Health Research, Ministry of Health and Family Welfare), August, 2013/Bhadra, 1935 (Saka), available at <http://164.100.47.5/newcommittee/reports/EnglishCommittees/Committee%20on%20Health%20and%20Family%20Welfare/72.pdf> (last accessed on June 2, 2018)

¹³² *Id.* ¶ 6.16, p. 11-12.

government led some women's health rights activists to take the case to court (hereafter called the *Kalpana Mehta* case). In 2010-2011, the women's rights activists and some lawyers organized a fact-finding mission in the two States where the HPV vaccination project was conducted. They visited schools where vaccinations were administered and conducted interviews with the wardens, teachers, students, and families. They investigated the informed consent process in a secondary school run by the government, where approximately 300 girls were vaccinated. The findings were reported in their PIL petition:

The girls were not informed of the nature or purpose of the vaccine. The girls did not know where the cervix is located and this had not been explained to them. The girls believed the vaccination was being administered by the government. Many girls felt it was compulsory to be vaccinated. They were not informed of any possible side-effects of the vaccine.¹³³

When the Supreme Court, in one hearing of the *Kalpana Mehta* case, asked the government to explain why no action had been taken against PATH or against the Bill and Melinda Gates foundation, the government furnished the following response:

As of now, there are no specific penalties for provisions relating to clinical trials under the Act. Therefore, as per the legal provisions prevalent at the point of time under the Act and pertinent rules, ICMR has already taken action admissible under these rules.¹³⁴

ICMR's action was to suspend the trial. To some commentators, the lack of penalising provisions for failure to adhere to ethical guidelines in clinical research was proof of the inadequacy of the Indian regulatory system in protecting research participants.¹³⁵

¹³³ *Kalpana Mehta & Ors. v. Union of India & Others*, W. P. (Civil) 558/2012, Supreme Court of India. Final Judgment of the case was delivered on April 5, 2017. A copy of the written book of petition with averments is available at the Human Rights Law Network (HRLN) website, at <http://www.hrln.org/hrln/images/stories/pdf/HRLN-HPV-SYNOP.pdf> (last accessed on June 2, 2018)

¹³⁴ U. Anand, 'Can't penalise US NGO for violating drug trial norms', THE INDIAN EXPRESS, (April 18, 2015).

¹³⁵ Nundy & Gulhati wrote an article in 2005 calling out the inadequacy of the Indian regulatory system. A decade after this, the regulatory system still showed no signs of significant change in terms of describing penalties for defaulting on ethical and legal requirements of clinical trials. See S. Nundy & C. M. Gulhati, *A New Colonialism? — Conducting Clinical Trials in India*, THE NEW ENGLAND JOURNAL OF MEDICINE, Vol. 352, (2005), pp. 1633-1636.

PATH had conducted the vaccination project in four developing countries, including India, Peru, Uganda and Vietnam. PATH employees asserted that the vaccination project was not a clinical trial for an untested drug. The aim of the study was to explore suitable strategies for vaccine delivery and to help national authorities in low and middle-income countries gain information regarding the feasibility of introducing the HPV vaccine to protect girls against HPV, which is the main cause for cervical cancer.¹³⁶ They also sought to clarify the “misreporting” done by commentators writing about the HPV case and asserted that the deaths that took place during the vaccination project were not caused due to the vaccine.¹³⁷ The study was conducted in collaboration with the Indian Council of Medical Research (ICMR), which is the apex body in India for the formulation, coordination, and promotion of biomedical research. The ICMR is responsible for the drafting and release of the guidelines for the ethical conduct of human subject research in India. When the irregularities in the HPV vaccination project became known, they suspended the project. The ICMR conducted its own inquiry and reported that:

[A] lot of negative vibe has been generated against this project due to mal-handling of the entire situation, but the committee has not been able to identify a single event, individual or agency which can be held entirely accountable for it.¹³⁸

ICMR found some discrepancies in the study, referring to inadequate consent procedures, which they said did not “appear to be wilful or fully anticipatable” but could be seen as a “learning experience”. They stressed the need for separate legislation covering all aspects of Biomedical and Health Research involving Human Participants, with particular emphasis on the “process of consent taking” and vulnerable research subjects.¹³⁹

¹³⁶ D. S. LaMontagne, et al., *Human Papillomavirus Vaccine Delivery Strategies that Achieved High Coverage in Low- and Middle-Income Countries*, BULLETIN OF THE WORLD HEALTH ORGANISATION, Vol. 89, (2011); D. S. LaMontagne & J. D. Sherris, *Addressing questions about the HPV vaccine project in India*, THE LANCET, Vol. 14, (November 2013), e492.

¹³⁷ *Id.*

¹³⁸ Indian Council of Medical Research (ICMR), Final Report of the Committee appointed by the Govt. of India, vide notification No. V.25011/160/2010 -HR dated 15th April, 2010, to enquire into “Alleged irregularities in the conduct of studies using Human Papilloma Virus (HPV) vaccine” by PATH in India, (February 15, 2011), available at <http://www.icmr.nic.in/final/HPV%20PATH%20final%20report.pdf> (last accessed on June 2, 2018)

¹³⁹ *Id.*, ¶ 8.8, p. 81.

The averments made in the SAM petition were that the three aforementioned trials, amongst others, were being conducted in the country because either they were not allowed outside India or because such trials were cost-prohibitive in the country of origin. The petition claimed that the poor, illiterate, and vulnerable sections of the society became subjects of these illegal trials. The petition also alleged that the doctors conducted these trials with the sole aim of making money and that the trials were conducted without any regard for the consent of the subjects. The petitioners asserted that the manner in which certain trials are conducted in India is in violation of Article 21 of the Constitution of India which states that “[n]o person shall be deprived of his life or personal liberty except according to procedure established by law”. The petition also claimed that the “inaction of the government” in not restricting these clinical trials is in violation of Article 14 of the Constitution which states that “[t]he State shall not deny to any person equality before the law or the equal protection of the laws within the territory of India”.

3.2.2. Relevance of these specific instances

In the three cases mentioned above, there was an issue with informed consent and the manner in which it was handled.

In 1) **Unethical Trials in Indore** the EOW case failed due to lack of a sufficient basis for a criminal proceeding. Nonetheless, the EOW report found discrepancies with the informed consent procedure and the doctors were punished in the form of a fine, even though the doctors involved refuted the allegations that the fines were for violating ethical procedures. However, no other action was taken against the doctors involved.

In 2) **Trials on the Bhopal Gas Victims in Bhopal** the trials were allegedly carried out on disaster victims who, according to the petitioners, had reduced autonomy because of their dependency on the hospital for the medical treatment that they needed as victims of the disaster. It was also alleged that they could not sign their own names. Here, the DCGI inquiry found that trials were conducted on disaster victims but trial casualties were not related to the trial. The petitioners challenged the

report findings because they were not independently verified. Again, no legal or other action was taken for violating informed consent procedures.

In 3) **The HPV vaccine (Gardasil and Cervarix) clinical trial** the petitioners alleged that PATH and the Bill and Melinda Gates Foundation, along with the drug producers, were involved in an unethical trial where informed consent procedures were violated. However, despite the fact that the Parliamentary Committee inquiry report also revealed irregularities in the informed consent procedures, no action was taken beyond a temporary suspension of the project.

It is evident that because of the lack of a clear law and regulatory practice it has been hard to apportion any blame or wrongdoing in legal terms, although in all the cases there was recognition that best practice had not been followed. All these cases suggest that ethical considerations and rules pertaining to informed consent fall outside the bounds of Indian law and enforcement. Although, as noted earlier, during the hearing of the SAM case the Supreme Court issued interim orders that prompted the CDSCO to introduce the requirement to make audio-video recording of informed consent mandatory for vulnerable subjects. Nevertheless, the success or failure of such a mandate is yet to be ascertained as the regulations are silent on the definition of vulnerable subjects, the vetting of consent tapes, and the repercussions if regulations are ignored or unmet.

3.3. Conclusion

This chapter aimed to show how the idea of informed consent translates to the Indian context. This, however, is an incomplete elucidation of how informed consent looks like within the Indian context. As noted above, problems with informed consent procedures exist partly because of the inadequacy of the existing regulatory framework to effectuate the idea of informed consent. The existing framework, i.e., the Indian law on informed consent, will be assessed in the next chapter.

LAW OF INFORMED CONSENT IN INDIA & ABROAD

4.0. Introduction

The idea of informed consent is made effective through the law of informed consent. As noted in the previous chapter, the legal doctrine of informed consent largely developed around the doctor-patient relationship in relation to the treatment context. In this chapter, I will assess the appropriateness of its applicability to the research context. This chapter aims to answer three questions: How does the law in India deal with informed consent in treatment and in clinical research? How can courts deal with instances of lack of informed consent in research? What are the limits of law in dealing with the informed consent process? To answer these, the chapter is divided into three parts. Part 1 gives a brief overview of the current Indian precedent dealing with the lack of informed consent within the treatment context. It also considers the feasibility of its applicability to the research context. Part 2 outlines the legal avenues available in India for addressing lack of informed consent in research. Due to the absence of case law on lack of informed consent in research in India, it also engages in a *normative* discussion, that is, a discussion on how the Indian legal doctrine of informed consent in clinical research can be developed around clinical research. Part 3 discusses the limits of law in dealing with informed consent in research within the larger social context of India.

Part 1. Law of Informed Consent in Treatment

4.1. Indian Law and the Treatment Context

Before we look at the specific legal cases dealing with informed consent in India, it is important to have a general idea of the Indian legal system. India follows the common law tradition like most of the countries that were a part of the British Commonwealth. The jurisprudence is said to mirror that of England, but one that is ‘cross-fertilized’ by Indian values that are reflected in the Constitution of India.¹ There is an established practice by the Indian courts, especially the Supreme Court of

¹ B. N. Srikrishna, *The Indian Legal System*, INTERNATIONAL JOURNAL OF LEGAL INFORMATION, Vol. 36, Issue No. 2, Article 8, (2008).

India, to consider foreign precedents for settling various conflicts in law, for interpreting identical provisions in law, or for establishing good practice.² It is crucial to note that the value of these precedents is ‘persuasive’ and not ‘binding’.³ In the past few years reliance on foreign precedents has become quite commonplace in common law jurisdictions like South Africa, India, and Canada. Some scholars have dubbed this trend as “trans-judicial communication”.⁴ This kind of communication involves judges citing relevant passages from both international and comparative law in their judgments. Indian courts have also referred to certain academic writings that have appeared in various law reviews of the American universities.⁵ Consequently, the law on informed consent in India has largely been shaped around judicial precedents from the UK and the US.

Here I will analyse how informed consent is understood in tort law in India. This is because other than the Consumer Protection Act, 1986 (CPA), where doctors are treated as *service providers* and patients as *consumers* of such services and lack of informed consent as *deficiency in service*, there is no other statutory basis for a lack of informed consent claim in treatment.⁶ The standards for information disclosure as developed in the torts of medical negligence and battery form the corpus of the legal doctrine of informed consent.

² M. N. Jha, India: *A three-tier judicial review system*, in: M. YILMAZ (ED.), DOMESTIC JUDICIAL REVIEW OF TRADE REMEDIES: EXPERIENCES OF THE MOST ACTIVE WTO MEMBERS, (Cambridge University Press, 2013), p. 287.

³ Chief Justice K.G. Balakrishnan, *The Role of Foreign Precedents in a Country's Legal System*, Lecture at Northwestern University, Illinois, (October 28, 2008), p. 11 available at [http://www.supremecourtindia.nic.in/speeches/speeches_2008/28\[1\].10.08_northwestern_university_lecture.pdf](http://www.supremecourtindia.nic.in/speeches/speeches_2008/28[1].10.08_northwestern_university_lecture.pdf) (last accessed on June 2, 2018)

⁴ A. Slaughter, *A typology of transjudicial communication*, UNIVERSITY OF RICHMOND LAW REVIEW, Vol. 29, (1994), pp. 99-137.

⁵ See R. Dhavan, *Borrowed Ideas: On the Impact of American Scholarship on Indian Law*, THE AMERICAN JOURNAL OF COMPARATIVE LAW, Vol. 33, Issue No. 3, (Summer 1985), pp. 505-526.

⁶ Consumer Protection Act, 1986, See (§) 2(d) for consumer, (§) 2(g) for deficiency of service, and (§) (o) for service. Furthermore, some states in the USA and Canada have specific statutes that deal with lack of informed consent in treatment, *see for example* Ontario's Health Care Consent Act, 1996, Louisiana's Medical Malpractice Act, 1975, and so on.

In tort law, a liability arises if a doctor fails in her duty to disclose the material risks inherent in the proposed therapeutic treatment or surgery.⁷ Thus, the patient has the common law right to recover damages against the physician for failure to provide adequate informed consent.⁸ A claim for lack of informed consent calls for the same elements required to establish a traditional negligence claim under tort law, viz.,

- i) a duty of care owed by a doctor to use reasonable care to prevent harm to the plaintiff,
- ii) breach of this duty of care,
- iii) harm or injury caused to the patient, and
- iv) a proximate causal link between the injury and the breach of duty.⁹

In this chapter I will predominantly focus on i), ii), and iii) - the duty owed by the doctor/investigator (this duty being duty to inform the individual of all material risks), breach of that duty in performing a medical/clinical intervention on the individual, and the resulting harm to the individual.

Lack of informed consent cases may also fall under the tort of trespass to persons, which is the tort of battery in India. Most torts fall under two categories -

⁷ Winfield, whose text-book might be well-known amongst tort-law students in India and abroad, notes that a "tortious liability arises out of breach of duty primarily fixed by the law: this duty is towards persons generally and its breach is redressible by an action for unliquidated damages. *See* P. H. WINFIELD, *A TEXT-BOOK OF THE LAW OF TORT*, (Sweet & Maxwell, 1954), *see also* V. G. Koch, *A Private Right of Action for Informed Consent in Research*, *STETON HALL LAW REVIEW*, Vol. 45, (2015), p 174.

⁸ *Id.*

⁹ J. W. BERG, ET AL., *INFORMED CONSENT: LEGAL THEORY AND CLINICAL PRACTICE*, (Oxford University Press, 2001), pp. 133-34. Depending on the jurisdictions, text-books, and scholarly works referred to, the elements required to prove medical negligence range from 3-5. Scholars in the US seem to find 5 elements in a negligence claim, viz., (1) duty, (2) breach, (3) cause in fact, (4) proximate cause, and (5) harm, giving reasons as to why some ideas in each cannot be conflated with other elements. But most traditional accounts in the UK (sometimes even in the US) consider 3 elements to be sufficient to bring a claim of negligence, viz., 1) duty, 2) breach of duty, 3) injury/harm proximately caused by such breach. *See* D. G. Owen, *The Five Elements of Negligence*, *HOFSTRA LAW REVIEW*, Vol. 35, Issue No. 4, (2007); R. Goldberg, *Medical Malpractice and Compensation in the UK*, *CHICAGO-KENT LAW REVIEW*, Vol. 87, Issue No. 1, (2012), p. 143. *See also* A. Meisel, *A "dignitary tort" as a bridge between the idea of informed consent and the law of informed consent*, *LAW MEDICINE AND HEALTH CARE*, Vol. 16, Issue No. 3-4, (1988), pp. 210-218.

intentional and unintentional torts.¹⁰ To put it simply, negligence is an unintentional tort where a patient is not *sufficiently* informed about the risks inherent in the treatment and alternatives to the treatment. Assault and battery are intentional torts where the doctor intended to cause contact with the patient *without the patient's consent*. A claim can be brought under the tort of battery if it involves any non-consensual touching. It is important to note the difference between these torts because there have been situations where a claim was erroneously identified under battery instead of negligence.¹¹ This often leads to dismissal of the case for inappropriate cause of action.

4.1.1. Indian case law on informed consent in treatment

The current binding precedent on informed consent in India is *Samira Kohli v. Dr. Prabha Manchanda & Another*¹² (hereafter the *Kohli* case). The brief facts of the case are that Samira Kohli, the petitioner, consulted with Dr. Prabha Manchanda, the respondent, regarding her prolonged menstrual bleeding. She was admitted to the respondent's clinic where she signed the consent form for hospital admission, medical treatment, and for surgery. The consent form for surgery described the procedure to be undergone by the petitioner as "diagnostic and operative laparoscopy. Laparotomy may be needed". The petitioner was subjected to a laparoscopic examination under general anaesthesia. While the petitioner was unconscious during her examination, the respondent's assistant took the consent of the patient's mother for a hysterectomy. After which the respondent removed the

¹⁰ See N. J. Moore, *Intent and Consent in the Tort of Battery: Confusion and Controversy*, AMERICAN UNIVERSITY LAW REVIEW, Vol. 61, Issue No.6, (2012), pp. 1585-1654.

¹¹ For instance, in *Chatterton v. Gerson*, [1981] 1 ALL ER 257, Mrs Chatterton had chronic pain issues from a post-operative scar, she consented to undergo surgery to alleviate the pain. The doctor did not inform her of the risk of permanent immobility in her limbs, which happened to one of her legs. She sued the doctor under the tort of battery claiming that her consent was not obtained due to failure of disclosure of risks. The Court held that her consent was real and that her claim could not lie under trespass to person (battery) since she had consented to the operation, although the court held that an action would "lie in negligence if there was a failure to inform the patient of the nature of the operation and its implications and the patient proved that, if a proper explanation had been given she would not have consented to the operation." The landmark Canadian case *Reibl v. Hughes* was another example of a mistaken case of battery when the cause of action lay under negligence, *infra* note 27.

¹² *Samira Kohli v. Dr. Prabha Manchanda and Another*, (2008) 2 SCC 1, also available at <https://indiankanoon.org/doc/438423/> (paragraph numbers correspond to the web print version).

patient's uterus (abdominal hysterectomy, AH), ovaries, and fallopian tubes (bilateral salpingo-oophorectomy, BSO). The petitioner filed a complaint before the National Consumer Disputes Redressal Commission (NCDRC) under the CPA, claiming compensation of INR 25 *lakh*¹³ from the respondent. Her complaint said that the doctor had been negligent, and that the radical surgery, by which her uterus, ovaries, and fallopian tubes had been removed, had been performed without her consent. The petitioner claimed compensation for the loss of her reproductive organs, irreversible damage to the body, loss of the opportunity to become a mother, diminished prospects of matrimony, and for emotional trauma. The NCDRC dismissed the complaint on the grounds that the hysterectomy had been performed with adequate care and that the patient had voluntarily sought treatment at the respondent's clinic. Aggrieved by the order, the petitioner filed an appeal in the Supreme Court of India. The court overruled the order passed by the NCDRC and held that:

...there was no consent by the appellant for performing hysterectomy and salpingo-oophorectomy, performance of such surgery was an unauthorized invasion and interference with appellant's body which amounted to a tortious act of assault and battery and therefore a deficiency in service.¹⁴

The court, however, observed that even though the respondent's act was in "excess of consent",¹⁵ the act was done in *good faith* and for the benefit of the petitioner. Consequently, the compensation amount that was directed to be paid to the petitioner was significantly less than claimed.¹⁶ The next section will look at the relevance of this case to the research context.

4.1.2. Importance of the *Kohli* case and its applicability to the research context

As noted in the previous chapter, *adequate information disclosure* is one of the three essential elements of informed consent. The chapter also detailed three distinct standards used by courts in different common law jurisdictions to assess information

¹³ A lakh is a unit of hundred thousand (100,000).

¹⁴ *Supra* note 12.

¹⁵ Meaning acts performed in excess of what was consented to or acts involving consent to only the partial procedure instead of the whole.

¹⁶ The petitioner was denied the entire fee charged for the surgery and was directed to pay INR 25,000 as compensation for the unauthorized AH-BSO surgery to the appellant.

disclosure - the professional practice standard, the reasonable person standard, and the less commonly used subjective standard. The *Kohli* case dealt with two of these standards: the professional practice standard, also known as the *Bolam* test, and the reasonable person standard, called the *Canterbury* principle. Let us look at these standards before evaluating the *Kohli* case.

The US Courts of Appeals, District of Columbia Circuit's decision in *Canterbury v. Spence*¹⁷ laid down the 'reasonable person standard', also called the *Canterbury* principle, which mandated the doctor to disclose all 'material risks' to a patient to indicate that the consent was 'informed'. The US court held that:

[t]rue consent to what happens to one's self is the informed exercise of a choice, and that entails an opportunity to evaluate knowledgeably the options available and the risks attendant upon each. The average patient has little or no understanding of the medical arts, and ordinarily has only his physician to whom he can look for enlightenment with which to reach an intelligent decision. From these almost axiomatic considerations springs the need, and in turn the requirement, of a reasonable divulgence by physician to patient to make such a decision possible.¹⁸

Thereafter the court laid down that the doctors had a duty to disclose all material risks to the patient with the exception of where disclosure of risks would pose a threat to the well-being of the patient. The court also defined 'material' risk; it held that a risk was material:

...when a reasonable person, in what the physician knows or should know to be the patient's position, would be likely to attach significance to the risk or cluster of risks in deciding whether or not to forego the proposed therapy.¹⁹

In contrast, the *Bolam* case (discussed below) took the view that a reasonable practitioner was in a better position to decide what information was relevant to be disclosed to the patient for her decision to proceed with the medical procedure.

¹⁷ *Canterbury v. Spence*, 464 F.2d 772 (D.C. Cir. 1972). In this case the plaintiff, Canterbury, claimed that prior to his spinal surgery, the defendant, surgeon Spence did not disclose the probable consequence of paralysis which the plaintiff later developed as a result of the surgery.

¹⁸ *Id.*

¹⁹ *Supra* note 17, *Canterbury* case.

The ‘professional practice standard’ for determining negligence and for assessing information disclosure was first developed in the UK case, *Bolam v. Friern Hospital Management Committee*.²⁰ In this case, the English High Court endorsed medical paternalism through its “doctor knows best” ratio. While discussing the issue of negligence in failing to obtain a minimum standard of care while treating the patient, Judge McNair wrote:

A doctor is not guilty of negligence if he has acted in accordance with the practice accepted as proper by a responsible body of medical men skilled in that particular art

While determining if the doctors were negligent in failing to warn the patient of the risks involved in the treatment, the English court upheld the verdict of Lord President Clyde in *Hunter v. Hanley*,²¹ which was:

That in determining whether or not the plaintiff was entitled to succeed on his allegation of failure to warn, the material considerations were, first, whether or not the defendants, in not warning him of the risks involved in the treatment, had fallen below a standard of practice recognized as proper by a competent body of professional opinion

The *ratio decidendi* in this case came to be known as the *Bolam* test and was cemented further in the House of Lord’s decision in *Sidaway v. Board of Governors of the Bethlem Royal Hospital*.²² (hereafter *Sidaway* case)

In *Sidaway* case, the claimant, Mrs. Sidaway, was left paralysed after a spinal surgery and she sued the hospital for not having been informed about the risk of complication, which was around 1-2%. The majority of the House of Lords applied the *Bolam test* and stated that it was the accepted medical practice to not disclose a paralysis risk in spinal surgeries because the risk was extremely low.²³ This case,

²⁰ *Bolam v. Friern Hospital Management Committee*, [1957] 1 WLR 582. In this case the claimant, Bolam, was undergoing electro convulsive therapy (ECT) as treatment for his mental illness. The doctor from the defendant Hospital did not give the claimant any relaxant drugs. During the ECT the claimant suffered a serious fracture. There was a divided opinion amongst medical professionals regarding administration of relaxant drugs during ECT. When relaxants were given there was a very small risk of death, but when they were not given there was a small risk of fracture. The claimant claimed that the doctor was in breach of duty for not using relaxant drugs during his ECT.

²¹ 1955 S.L.T. 213, 217.

²² *Sidaway v. Board of Governors of the Bethlem Royal Hospital*, [1985] AC 871.

²³ *Id.*, pp. 904-905.

even though rejected by the courts in the US, Canada, and Australia, prevailed in the UK for over 30 years. The position it upheld was that the *Bolam test* applied not only to a doctor's decisions about diagnosis and treatment but also to a doctor's advice and disclosure for the purpose of patient's consent. However, the case became well-known for Lord Scarman's dissenting opinion, which was heavily influenced by the views of his transatlantic counterparts,²⁴ and read:

That [Bolam] test, while correct with regard to diagnosis and treatment—matters of professional skill and competence—is not correct with regard to warnings. Having ascertained the risks attendant upon proposed treatment, the duty to give information as to those risks is an adjunct of the patient's right to decide. The duty is to tell the patient the material risks and the choices open to him. Where an operation is on the fringe of necessity, the duty of disclosure of risks should be greater.²⁵

He suggested that the appropriate test would be the one propounded by Judge Bristow in *Chatterson v. Gerson*,²⁶ who had adopted the position of the Canadian case, *Reibl v. Hughes*.²⁷ Judge Bristow wrote of the duty of the doctor that:

[h]e ought to warn of what may happen by misfortune however well the operation is done, if there is a real risk of a misfortune inherent in the procedure.

It is pertinent to note that the English courts have now moved beyond the *Bolam* test and the *Sidaway* decision. In a 2015 case, *Montgomery v. Lanarkshire Health Board*,²⁸ the UK Supreme Court, while deciding on the issue of whether a consultant obstetrician and gynaecologist was negligent in managing the pregnancy of Mrs. Montgomery, made way for a fresh legal understanding of the concept of informed consent. The seven Judge Bench allowed Mrs Montgomery's appeal and after a

²⁴ He referred to the US case *Canterbury v. Spence*, *supra* note 17, and the Canadian case *Reibl v. Hughes*, *infra* note 27.

²⁵ *Supra* note 21, p. 874.

²⁶ *Supra* note 12.

²⁷ In *Reibl v. Hughes*, [1980] 2 SCR 880, the Canadian Supreme Court, other than laying down the difference between battery and negligence, rejected the "accepted medical practice" test for disclosure of information and held that the test to ascertain if enough information has been given to a patient was to objectively consider if a reasonable person in the plaintiff's position would have decided to have the surgery if they were given all of the information and to also consider if this answer was different than the original answer with only the amount of information that was given.

²⁸ [2015] 2 WLR 768.

careful analysis of the post-*Bolam* cases on informed consent overturned the *Sidaway* judgment. Following *Montgomery*, “the *Bolam* test will no longer apply to disclosure for consent and is replaced with quite another, namely the so-called patient-centred test.”²⁹ This means that, in the UK, the standard has shifted from the paternalistic ‘what a reasonable practitioner would do’ to a patient-autonomy enhancing ‘what a reasonable person would want to know?’

The *Kohli* case is noteworthy for the jurisprudence on informed consent in India for two reasons: 1) It rejects the *Canterbury* principle, or the reasonable person standard, for information disclosure that most leading common law jurisdictions have now accepted and 2) it adopts a socio-economic line of reasoning to prefer the *Bolam* test over *Canterbury*. The judges in this case noted:

In India, [the] majority of citizens requiring medical care and treatment fall below the poverty line. Most of them are illiterate or semi-literate. *They cannot comprehend medical terms, concepts, and treatment procedures.* They cannot understand the functions of various organs or the effect of removal of such organs. They do not have access to effective but costly diagnostic procedures. Poor patients lying in the corridors of hospitals after admission for want of beds or patients waiting for days on the roadside for an admission or a mere examination, is a common sight. For them, any treatment with reference to rough and ready diagnosis based on their outward symptoms and doctor's experience or intuition is acceptable and welcome so long as it is free or cheap; and whatever the doctor decides as being in their interest, is usually unquestioningly accepted. *They are a passive, ignorant and uninvolved in treatment procedures.*³⁰ [My emphasis]

This line of reasoning, where poverty and poor conditions of literacy are automatically assumed to render an individual ‘passive’ and ‘ignorant’ about one’s treatment decisions, is dangerously paternalistic. Although the judges in the *Kohli* case have shown great awareness and sympathy for the *real* conditions of patients in India, they have reiterated the support for paternalism that the *Bolam* test seemed to

²⁹ J. Badanoch QC, *A doctor’s duty of disclosure and the decline of ‘The Bolam Test’: A dramatic change in the law on patient consent*, MEDICO-LEGAL JOURNAL, Vol. 84, Issue No. 1, (2016).

³⁰ *Kohli* case, *supra* note 12, ¶ 26.

exemplify with its “doctors know best” approach.³¹ While making observations about the appalling conditions of patients in India, the judges in this case also questioned the relevance of informed consent in a country like India. They opined:

The poor and needy face a hostile medical environment inadequacy in the number of hospitals and beds, non-availability of adequate treatment facilities, utter lack of qualitative treatment, corruption, callousness and apathy. Many poor patients with serious ailments (e.g. heart patients and cancer patients) have to wait for months for their turn even for diagnosis, and due to limited treatment facilities, many die even before their turn comes for treatment. What choice do these poor patients have? Any treatment of whatever degree, is a boon or a favour, for them. *The stark reality is that for a vast majority in the country, the concepts of informed consent or any form of consent, and choice in treatment, have no meaning or relevance.*³² [My emphasis]

The conclusion of the Court here is problematic on at least two grounds. First, informed consent is not a conditional right. Saying that informed consent has “no meaning or relevance” for the poor owing to the lack of treatment facilities implies that informed consent is a *luxury* afforded to those who are not poor and have access to medical facilities. Yet all patients and research subjects, whether rich or poor, have the right to be informed about the treatment or study and have the right to either consent or to not consent depending on that information. Second, the judges in this case lost an excellent opportunity to reaffirm the duty of care owed to patients irrespective of their backgrounds. Even though the premise of the entire paragraph is true, and shows that the judges are aware of the ground realities in India, the conclusion ought to have been in favour of the protection of every patient’s autonomy. If this reasoning were to be extended to the research context, it would not stand, as no one would condone a position that informed consent has no meaning or relevance for the poor people volunteering for clinical research. In fact, the situation is quite the opposite for research; there is a need for bettering the informed consent process to protect the poor and vulnerable. For now, when the time comes for the

³¹ The Bolam test has been derided in its support for medical paternalism in almost all scholarly works pertaining to the evolution of the law of informed consent, see K. McCombe, *Paternalism and consent: has the law finally caught up with the profession?*, ANAESTHESIA, Vol. 70, (2015), pp. 1016–1019; A. Lee, *‘Bolam’ to ‘Montgomery’ is result of evolutionary change of medical practice towards patient-centred care*, POSTGRADUATE MEDICAL JOURNAL, (2016), pp. 1-5.

³² *Supra* note 12.

courts to deal with cases arising out of lack of informed consent in research in India, they will first look at the law of informed consent within the treatment context to draw parallels with the research context, and here they would find an obiter that called informed consent meaningless and irrelevant for poor patients.

On the matter of informed consent from the perspective of the ‘takers of consent’, the judges in the *Kohli* case opined:

The position of doctors in government and charitable hospitals, who treat them, is also unenviable. They are overworked, understaffed, with little or no diagnostic or surgical facilities and limited choice of medicines and treatment procedures. They have to improvise with virtual non-existent facilities and limited dubious medicines. They are required to be committed, service oriented and non-commercial in outlook. *What choice of treatment can these doctors give to the poor patients? What informed consent can they take from them?*³³ [My emphasis]

Although the premise of this paragraph is sympathetic, the Court’s observations lead to unsound implications. If this rhetorical observation by the court were to be advanced further, it would mean that the lack of resources available to a doctor would absolve the doctor from the duty to take informed consent from her patients. If this reasoning were to be extended to the research context, it would mean absolving researchers from their duty to take informed consent because of time constraints, funding problems, lack of administrative support, etc. This, however, is neither the established legal position, nor the ethical one. Fortunately, these observations were made as *obiter dicta*, subsequent to which the court chose *Bolam* over *Canterbury* citing the “ground realities” in India. It said:

We have, however, consciously preferred the ‘real consent’ concept evolved in *Bolam* and *Sidaway* in preference to the ‘reasonably prudent patient test’ in *Canterbury*, *having regard to the ground realities in medical and health-care in India*. But if *medical practitioners and private hospitals* become more and more commercialized, and if there is a corresponding increase in the awareness of patient’s rights among the public, inevitably, a day may come when we may have to move towards *Canterbury*. But not for the present.³⁴ [My emphasis]

³³ *Id.*, ¶ 27.

³⁴ *Id.*, ¶ 33.

This reasoning is equally questionable. This implies that for the court to have considered an autonomy-enhancing standard of information disclosure there would need to be some evidence that Indian citizens were more aware of their rights as patients. This leads to the implication that *poor* and *unaware* patients do not require a stronger protection of their right to autonomy and informed consent unless commercialisation of medicine become commonplace. If we look at the research context in India, we will find that most privately sponsored clinical research is commercial by nature and not all participants are aware of their rights.³⁵ Nevertheless, the difference between research and treatment is such that the unaware participants need to be given more information related to the study by the researcher.

The *Bolam* test in affirming that the “doctor knows best” is quite redundant for the research context as it goes both against the ethical guidelines as well as informed consent process required by the statute.³⁶ Albeit the researcher/investigator of a study might “know best” he is nonetheless required to disclose all relevant information about the study to the participant. Such disclosure cannot be measured against what other professionals in the field do considering that every research study is different. Furthermore, the risks involved in most studies are unknown; in fact, most studies are conducted on human subjects to uncover risks involved in procedures or drugs. Therefore, the potential risks that are generally disclosed in a similar study of a similar drug might be completely different from potential risks involved in the study of another. As such, and by the farthest stretch, if the courts were to consider the *Bolam* test as applicable to the research context, they could look at the ICMR or GCP ethical guidelines as the professionally accepted standards in human subject research. Given that most guidelines are released by professional bodies headed by people from a given profession, they can safely be regarded as the

³⁵ See V. D. Joshi, et al., *Public awareness and perception of clinical trials: Quantitative study in Pune*, PERSPECTIVES IN CLINICAL RESEARCH, Vol. 4, Issue No. 3, (2013); S. Nadimpally & D. Bhagianadh, “*The invisible*”: *Participant's experiences in clinical trials*, PERSPECTIVES IN CLINICAL RESEARCH, Vol. 8, Issue No. 1, (2017).

³⁶ The purpose of informed consent in research is to diminish power asymmetries where the researcher has all the information regarding a particular study and the research subject has none and where the research subject often receives no direct benefit from participation in the study (in cases of non-therapeutic research). See ICMR, Ethical Guidelines on Medical and Health Research on Human Participants, 2017, available at https://icmr.nic.in/guidelines/ICMR_Ethical_Guidelines_2017.pdf (last accessed on July 5, 2018) and Schedule Y of Drugs and Cosmetics Rules, 1945.

codified norms that ought to govern the behaviour of those professionals. This is perhaps the only approach that could somehow accommodate the *Bolam* test within the research context.

Let us now look at another reason given by the court in the *Kohli* case to prefer the *Bolam* test to the *Canterbury* principle, the court noted:

People in India still have great regard and respect for Doctors... There is an atmosphere of trust and implicit faith in the advice given by the Doctor. The Indian psyche rarely questions or challenges the medical advice. Having regard to the conditions obtaining in India, as also the settled and recognized practices of medical fraternity in India, we are of the view that to nurture the doctor-patient relationship on the basis of trust, the extent and nature of information required to be given by doctors should continue to be governed by the *Bolam* test rather than the 'reasonably prudent patient' test evolved in *Canterbury*. It is for the doctor to decide, with reference to the condition of the patient, nature of illness, and the prevailing established practices, how much information regarding risks and consequences should be given to the patients, and how they should be couched, having the best interests of the patient.³⁷

All the justifications given by ethical theorists to strengthen informed consent by increasing dialogue between doctor-patient/researcher-research subject, such as protection of patients/subjects and restoration of trust, were taken by the judges in this judgment and formulated into reasons for supporting the paternalistic *Bolam* test. The court reiterated the paternalism, that has been now been rejected by most common law jurisdictions, in stating that for the Indian patient a doctor should make decisions as other doctors see fit. One cannot help but note that there was not one sound legal reason given by the Supreme Court not to opt for the pro-patient *Canterbury* principle. Perchance the judges should have taken note of the comments made by Shepherd et al, regarding legal justice in favour of patient rights; they wrote:

Law, especially in the realm of litigation, involves questions of justice. It can be no more pro-patient than it can be pro-plaintiff or pro-defendant. But if we return to the idea of patients generally - rather than the specific patient - being benefited or at least not harmed by a particular ruling, or to the idea of law that supports healing

³⁷ *Supra* note 12, ¶ 31.

relationships, then an explicit normative stance in favour of patients does not seem quite so out of keeping with more general notions of legal justice.³⁸

A final aspect of the *Kohli* case worthy of note is that the court used this case as an opportunity to clarify its position on medical negligence and the test for information disclosure, but it imposed liability on the respondent under the tort of battery.

The tort of battery can be defined as a “direct act of the defendant which has the effect of causing contact with the body of the plaintiff without the latter's consent.”³⁹ Thus, in order for a tort of battery to be established two conditions must be met, viz., i) intentional unauthorised contact with the patient (trespass to person) and ii) lack of patient's consent. It is pertinent to note that ‘harm’ is not a necessary condition for an action under battery. A patient can recover for battery even if she is not harmed, provided that the doctor performs the medical intervention without the patient's knowledge.⁴⁰ Referring to some established precedents regarding the tort of battery,⁴¹ the judges in the *Kohli* case held that:

Consent given only for a diagnostic procedure, cannot be considered as consent for therapeutic treatment. Consent given for a specific

³⁸ L. Shepherd & M. A. Hall, *Patient-Centered Health law and Ethics*, WAKE FOREST LAW REVIEW, Vol. 45, (2010), p.1450, while also citing J. H. Krause, *Can Health Law Truly Become Patient-Centered?*, WAKE FOREST LAW REVIEW, Vol. 45, Issue No. 107, (2010), pp. 1490-1492.

³⁹ F. A. Trindale, *Intentional Torts: Some Thoughts on Assault and Battery*, OXFORD JOURNAL OF LEGAL STUDIES, Vol. 2, (1982), pp. 211-237, p. 216.

⁴⁰ D. B. DOBBS, *DOBBS' LAW OF TORTS*, (2nd edn., West 2014).

⁴¹ The court referred to the *Canterbury* case, *supra* note 17, and also to the book, A. Grubb, *Principles of Medical Law*, (2nd edn., Oxford University Press), ¶ 3.04, p. 133, which explained that “[a]ny intentional touching of a person is unlawful and amounts to the tort of battery unless it is justified by consent or other lawful authority.” The judges cite *Murray v. McMurchy*, 1949 (2) DLR 442, BC, where the supreme court of British Columbia in Canada, was looking at a claim under battery. In this case, during the course of a patient undergoing caesarian section, the doctor found fibroid tumours in the patient's uterus. Concluding that such tumours would be a danger in case of a future pregnancy, the doctor performed a sterilization operation. The court upheld the claim for damages for battery and held that sterilization could not be justified under the principle of necessity, as there was no immediate threat or danger to the patient's health or life, and there only consent for C section not for sterilization. Similarly it considered the case, *Marshall v. Curry*, 1933 (3) DLR 260, in Canada. In this case the doctor discovered a diseased testicle while performing a hernia operation. The doctor considered the testicle to be gangrenous, which posed a threat to patient's life and health. The doctor removed the testicle without consent. Here the claim under battery failed because it was necessary to save the person's life despite no consent for the act.

treatment procedure will not be valid for conducting some other treatment procedure.⁴²

Thus, the court in the *Kohli* case held that the lack of consent for hysterectomy and SPO was “an unauthorized invasion and interference with appellant's body”, thereby holding the respondent liable under the tort of battery.

The *Kohli* case is the current precedent that stands as the law of informed consent in India; so far, it has not been challenged.⁴³ Briefly, the court held that a reasonable practitioner should decide what a patient must know regarding her treatment rather than the patient herself because Indian patients are poor and deeply trust their doctors. Therefore, in order to nurture the trust between the poor Indian patient, who is lucky enough to get any treatment, and the doctor, who is overworked, the *Bolam* test was more suited to the Indian reality.

Bearing in mind the law of informed consent in the treatment context in India, I will now analyse the legal avenues available for dealing with lack of informed consent in the research context in India.

Part 2. Law of Informed Consent for Research

There is no *established* legal doctrine of informed consent in research yet in India. Not the kind where courts have established comprehensive tests or standards for adjudicating claims arising from lack of informed consent in research. Nevertheless, if case law from other leading common law jurisdictions is taken into consideration, it can be said that the development of such doctrine is at its nascent stage. Therefore, in the absence of an established doctrine, I will first look at the possible legal avenues that are available to deal with lack of informed consent in research within the Indian context. After this, I will look at how the doctrine is being developed in other common law jurisdictions and how this could apply in India.

⁴² Kohli case, *supra* note 12, ¶ 32 (iii).

⁴³ Most recently, this case was used as the standard for medical negligence cases arriving before the National Commission in: *Vimhans Hospital and Ors. v. Anand Kumar Jha and Ors.* (2015), brought before the NCDRC.

4.2. Legal Avenues For Lack of Informed Consent in Research

Within the context of globalised clinical trials (GCTs), the multiplicity of parties involved in the process of clinical research poses a major problem - on whom must the liability rest? Should it rest on the global research sponsors, the Contract Research Organisations (CROs), the Ethics Committees (ECs), the hospitals or physicians involved, the investigators, and/or on all of them? Once the bearer(s) of liability is/are recognised, under what law does one challenge a violation of informed consent? Must it be a tort claim, a violation of a fundamental right, a criminal offence, or a breach of legal rights under administrative law⁴⁴ (that may arise where ‘public servants’ involved)? I do not discuss fixation of liability in this thesis, but as investigator/researcher perspectives are central to this thesis, I will assume that the investigator of a trial is the duty-bearer and a breach of duty to fully inform the trial participant could lead to a cause of action against her. The legal treatment of informed consent, in terms of post-fact remedy, is quite ambiguous despite it being a seemingly well-defined legal right. Listed hereunder (Sections 3.2.1 – 3.2.6) are the legal avenues that deal with informed consent in research. I will assess the legal treatment afforded to lack of informed consent cases under each.

4.2.1. Drugs and Cosmetics Act, 1940

As noted in the introductory chapter, the statute dealing with clinical trials in India is the Drugs and Cosmetics Act, 1940 (read with the Drugs and Cosmetics Rules, 1945). Schedule Y of the Act lays down the procedure for informed consent, which it considers as a necessary condition for conducting trials.⁴⁵ It says informed consent must be:

- i) Freely given and must be obtained in writing on an informed consent form.

⁴⁴ Administrative law mainly deals with the legal control of the government or of administrative authorities by the court. Articles 32 and 226, Constitution of India, deal with the power of the Supreme Court and High Courts respectively to issue orders or writs against administrative bodies. *See further* V. S. Deshpande (revised by V. Vahini), *Administrative Law*, in: J. MINATTUR (ED.), *THE INDIAN LEGAL SYSTEM*, (2nd edn., Indian Law Institute, 2006), p. 333-390.

⁴⁵ Schedule Y, The Drugs and Cosmetics Rules, 1945.

- ii) The Investigator must have provided information in a nontechnical and understandable manner.⁴⁶
- iii) The patient information sheet as well as the informed consent form should have been approved by the ethics committee and furnished to the Licensing Authority (DGCI).
- iv) In cases of incapacitated persons⁴⁷ consent may be obtained from a legally acceptable representative.⁴⁸
- v) If the trial participant or his/her legally acceptable representative is unable to read/write, an impartial witness should be present during the entire informed consent process who must append his/her signatures to the consent form.

Although Schedule Y talks about the procedure of informed consent in clinical trials, it does not specify the penalty or the repercussions to be meted out if the rule were to be ignored. The Government of India introduced penal provisions in the Drugs and Cosmetics (Amendment Bill) 2013, which prescribed imprisonment of up to two years for failing to conduct trial with the “conditions and permissions” of the central licensing authority and for not compensating trial related injuries.⁴⁹ However, the government withdrew the Amendment bill in 2016.⁵⁰ As of now, the old Act of 1940 still stands with no penal provisions.

⁴⁶ The Rules say that the Investigator must have informed the study subject verbally and through the patient information sheet (PIS).

⁴⁷ The Rules give example of an unconscious person or a minor or those suffering from severe mental illness or disability.

⁴⁸ The Rules says that a legally acceptable representative is a person who is able to give consent for or authorize an intervention in the patient as provided by the law(s) of India, viz., guardian for a minor and legal curator for the mentally ill and disabled.

⁴⁹ “Under section 4ZE of the Bill, any clinical researcher (including the sponsor, institution or investigator and anyone who works on their behalf) who fails to conduct a clinical trial in accordance with “the conditions of permission” imposed by the central licensing authority would be punishable with a minimum of two years’ imprisonment and a fine of ₹5 lakh. Additionally, under section 4ZG of the Bill, any researcher who fails to provide compensation to a subject suffering a trial-related injury shall be punishable with “imprisonment which may extend to two years and a fine which shall not be less than twice the amount of the compensation””, see M. Barnes, et al., *Clinical Trial Research Is No Crime*, THE HINDU BUSINESSLINE, (December 1, 2014), available at <http://www.thehindubusinessline.com/opinion/clinical-trial-research-is-no-crime/article6652150.ece>

⁵⁰ The old bill was withdrawn to review the old law to “facilitate ease of doing business” in the country and to enhance the “quality and efficacy of the products”. The Ministry of Health and Family Welfare (MoHFW) is set to “frame separate rules under the existing Act for regulating medical

If there are no penal provisions under the Act, one might then wonder how ethical lapses in research are usually dealt with. For that we will have to turn to the Code of Medical Ethics Regulation released by the Medical Council of India.

4.2.2. Ethical Misconduct

Given that the principal statute governing clinical trials in India does not have a penalty clause for lack of informed consent, it is necessary to look to other legal avenues available under related laws and regulations. Provision 7.22 of the Code of Medical Ethics Regulation, 2002, states:

Clinical drug trials or other research involving patients or volunteers as per the guidelines of ICMR can be undertaken, provided ethical considerations are borne in mind. Violation of existing ICMR guidelines in this regard shall constitute misconduct. Consent taken from the patient for trial of drug or therapy which is not as per the guidelines shall also be construed as misconduct.⁵¹

This means that if a registered doctor conducting a clinical trial in India fails to adhere to the ICMR Guidelines⁵² on ethical conduct for human subject research, including informed consent requirements, she could be deemed guilty of ‘professional misconduct’. As noted in the introductory chapter, disciplinary action has been taken by the Medical Council of India (MCI) against doctor-investigators guilty of ethical misconduct in clinical research.⁵³

devices; and (ii) to bring out separate legislations for regulating medical devices and Drugs and Cosmetics. *See* Press Information Bureau, Government of India Cabinet, Withdrawal of the Drugs and Cosmetics (Amendment) Bill, 2013 (June 22, 2016), available at

<http://pib.nic.in/newsite/PrintRelease.aspx?relid=146413> (last accessed on June 2, 2018)

⁵¹ Medical Council of India, Code of Medical Ethics Regulation, 2002, (Amended upto 8th October, 2016), Part III, Section 4 of the Gazette of India, dated 6th April, 2002)

<https://www.mciindia.org/ActivitiWebClient/rulesnregulations/codeofMedicalEthicsRegulations2002> (last accessed on June 2, 2018)

⁵² Indian Council of Medical Research (ICMR), Ethical Guidelines for Biomedical Research on Human Participants, 2006, (although an updated version was released in 2016, it is not available on the ICMR website yet), http://www.icmr.nic.in/ethical_guidelines.pdf (last accessed on June 2, 2018)

⁵³ Times News Network, *Two GMC docs suspended for illegal clinical trials*, (September 25, 2015), available at <http://timesofindia.indiatimes.com/city/goa/Two-GMC-docs-suspended-for-illegal-clinical-trials/articleshow/49096661.cms> (last accessed on June 2, 2018)

Nevertheless, for some instances of unethical research disciplinary action might not be enough. So is there any scope for criminal prosecution? The next section will briefly address this possibility.

4.2.3. Criminal Prosecution

If trial investigators were to use ‘criminal force’ to recruit trial participants in trials without their consent, a criminal liability could arise under Section 350 of the IPC.⁵⁴ A trespass to person, without a person’s consent can also be treated as a crime of ‘assault’ under Section 351 of the IPC.⁵⁵ No criminal liability arises in case of death or injury to participants, who duly consented, during the course of a clinical trial.⁵⁶ In cases where trial participation with the consent of the participant causes death or injury, or serious and adverse events (SAEs), due compensation has to be paid to the victim’s family under the provisions of the Drugs and Cosmetics Act, 1940, and in accordance with the compensation guidelines released by the CDSCO.⁵⁷ However, criminal liability could conceivably arise where trial participation, without the

⁵⁴ § 350, Indian Penal Code, 1860, defines Criminal Force as, “[w]hoever intentionally uses force to any person, without that person’s consent, in order to the committing of any offence, or intending by the use of such force to cause, or knowing it to be likely that by the use of such force he will cause injury, fear or annoyance to the person to whom the force is used, is said to use criminal force to that other”

⁵⁵ § 351, Indian Penal Code, 1860, says “[w]hoever makes any gesture, or any preparation intending or knowing it to be likely that such gesture or preparation will cause any person present to apprehend that he who makes that gesture or preparation is about to use criminal force to that person, is said to commit an assault”

⁵⁶ This aspect led Richardson to argue for considering criminal punishment for medical researchers involved in human experimentation, as according to him their “exalted social status and the perceived social benefit” of their research immunises them from criminal sanctions. For him, this negatively affects the value of autonomy and human dignity in research because alternative sanctions lack the same expressive impact as a criminal sanction. See L. S. Richardson, *When Human Experimentation is Criminal*, JOURNAL OF CRIMINAL LAW AND CRIMINOLOGY, Vol. 99, Issue No. 1, (2008-2009).

⁵⁷ Vide notification G.S.R. 53 (E) dated 30/01/2013 an amendment was made to Rule 122DAB and a new Appendix-XII was added to Schedule Y of the Drugs and Cosmetics Act, 1940. The amendment specified the procedure to arrive at the cause of death or injury to the subject, and to determine the quantum of compensation. A formula for compensation was later released by the CDSCO, available at <http://www.cdsco.nic.in/writereaddata/formula2013SAE.pdf> (last accessed on June 2, 2018)

consent of a person, and/or conducted by unregistered sponsors/investigators as a fraud trial, leads to the death of the trial participant.⁵⁸

Criminal liability aside, for unethically conducted trials the narrative is often framed in terms of violation of rights; something like due to improper informed consent procedure the *right of the research participant* was violated in a trial. The next section will examine this as a potential violation of a fundamental right as enshrined in the Constitution of India.

4.2.4. Violation of a fundamental right under the Constitution of India

If we frame informed consent within the narrative of *rights*, a research participant's right to informed consent can broadly be placed under the right to autonomy.⁵⁹ The Constitution of India provides for protection of 'personal liberty' under Article 21,⁶⁰ which also includes protection of personal autonomy. The Supreme Court has held personal liberty and autonomy to include "both the negative right of not to be subject to interference by others and the positive right of individuals to make decisions about their life, to express themselves and *to choose which activities to take part in.*"⁶¹ Constitutional rights are usually enforceable by an individual 'vertically' against state authorities. But constitutional courts in different jurisdictions have allowed for application of rights 'horizontally', which means that an individual may enforce constitutional rights against non-state private bodies.⁶² I make this point to suggest that if a claim based on the violation of the right to informed consent were brought before the courts⁶³ in India, as a violation of right to life and personal liberty, it

⁵⁸ This is slightly a hedging bet kind of a scenario, it could happen that in a fraud trial where the death of a non-consenting participant takes place, the provisions of the Indian Penal Code related to culpable homicide, murder, and fraud would be invoked.

⁵⁹ Of course, such a right to autonomy or the right to informed consent are not absolute. See C. P. Selinger, *The right to consent: Is it absolute?*, BRITISH JOURNAL OF MEDICAL PRACTITIONERS, Vol. 2, Issue No. 2, (2009), pp. 50-54.

⁶⁰ Article 21, Constitution of India, 1949, says "[n]o person shall be deprived of his life or personal liberty except according to a procedure established by law."

⁶¹ Anuj Garg v. Hotel Association of India, (2008) 3 SCC 1, ¶34-35 [My emphasis].

⁶² See S. Gardbaum, *The "Horizontal Effect" of Constitutional Rights*, MICHIGAN LAW REVIEW, Vol. 102, Issue 387, (2003).

⁶³ In India, the High Courts of various states and the Supreme Court have the jurisdiction to hear cases on violation of fundamental rights. See S. CHOUDHARY, ET AL., (EDS.), OXFORD HANDBOOK OF THE INDIAN CONSTITUTION, (Oxford University Press, 2016)

would, in the first instance, only be maintainable against ‘state’ actors.⁶⁴ However, the Supreme Court could impose an obligation upon the ‘state’ to take necessary steps to ensure the observation of fundamental rights by other private individuals. Therefore, it is important that we understand what ‘state’ means within the purview of this thread.

Article 12 of the Constitution of India defines ‘State’. It provides that “[s]tate includes the Government and Parliament of India and the Government and the Legislature of each of the States and all local *or other authorities* within the territory of India or under the control of the Government of India.”⁶⁵ But if ‘horizontality’ is

⁶⁴ Unless otherwise the claimants could prove that the body they brought the claim against was so close to a state body in structure and function that it be regarded as ‘state’ for purposes of enforcement of fundamental rights, *see infra* note 65. As far as maintainability of such a claim is concerned, it could fall under a tort claim of suing the state via vicarious liability. The Supreme Court has recognised in *State of Rajasthan v. Vidyawati*, AIR 1962 SC 933, that State is liable for the tort or wrongs committed by its officials. Moreover, in *Rudal Shah v. State of Bihar*, AIR 1983 SC 1086, the court held that the violation of right to life and personal liberty could end in civil liability. In fact, some commentators claim that it could be more expedient to make tort claims in India under Article 32 of the Constitution of India, (the provision whereby individuals may seek redressal for the violation of their fundamental rights), provided a government official has violated the fundamental right of occurred. *See* N. Mitra, Chapter 54: *Sovereign Immunity*, in: CHOUDHARY, ET AL., (EDS.), (2016), p. 996, *Id.*

⁶⁵ Article 12, Constitution of India, 1949, [My emphasis]. The Supreme Court has applied horizontality by including certain private bodies under ‘other authorities’, these bodies, in order to be considered ‘state’, ought to resemble state bodies in either their ‘structure’ or ‘function’ and should be closely connected to the State. Fundamental rights are generally regarded as *negative* rights; this means that they cast some constraints upon the actions of the State. They normally do not impose *positive obligations* upon the State to act in a particular way. However, the Supreme Court of India has imposed positive obligations upon the State to regulate acts of private individuals. This could be regarded as an application of horizontality through imposition of positive obligations. For instance, in the case of *Vishaka & Ors. v. State of Rajasthan & Ors.*, (1997) 6 SCC 241, where the court held that the State’s failure to pass a sexual harassment legislation for regulating public and private workplaces violated the constitutional and fundamental rights of the petitioner under Articles 14, 19 and 21. The Court issued a set of guidelines that were supposed to stand-in till the Parliament passed a legislation against sexual harassment. The guidelines imposed a positive obligation upon the state to enforce a negatively worded right and regulate actions of private workplaces. It is noteworthy that in this case, and in all other cases where obligations have been extended to private actors, the respondent has always been the State. The Indian Constitution allows for direct horizontality under three Articles protecting fundamental rights of the citizens; Article 15(2), wherein no citizen may be restricted from access to shops, public restaurants, hotels and places of public entertainment, as well as places of public resort dedicated to the use of the general public, on grounds only of religion, race, caste, sex, place of birth, or any of them. Article 17 prohibits the practice of untouchability and Article 23 which prohibits trafficking in human beings, as well as bonded labour. *See further* *Indian Medical Association v. Union of India*, (2011) 7 SCC 179, where private schools were ruled to be subject to

applied, which the Supreme Court has shown an inclination towards⁶⁶ but not quite fully endorsed for some rights,⁶⁷ the enforcement of fundamental rights could perhaps, someday, be directly extended to private non-state actors. As for now, the remedial avenue available by invoking fundamental rights enshrined in the Constitution of India is two-fold - (A) to plead a writ against the state,⁶⁸ or (B) demand compensation from a government official, who in the process of doing her official duty, violated a right that harmed the individual.⁶⁹

The first avenue, (A), was chosen by the petitioners in the *SAM case*, as was mentioned in the introductory chapter. It must be noted that a violation of informed consent norms was not a cause of action in the *SAM case* and the petitioners sought a writ, in public interest, against the state bodies.⁷⁰ It remains to be seen what a court would do where an *individual* (or a single person's) petition claimed a violation of the right to life due to a lack of informed consent in clinical trial participation. The court could, and probably might, direct the state to take steps towards controlling further violation of fundamental rights. Under the second avenue, (B), damages can be claimed by a broader application of tort law against the state (via vicarious liability). But such a claim would require the proof that the violator was performing an act in her official capacity, in the employment of the state, and her act in such capacity violated the fundamental right of the individual which led to harm or injury.⁷¹ This claim would be impossible to bring in a clinical trial organised and

the non-discrimination guarantees given by the Constitution, and *P.U.D.R. v. Union of India*, A.I.R. 1982 S.C. 1473, began" under Article 23 did not simply refer to "bonded labour" in its technical sense, i.e., inter-generational captivity, but "every form of forced labour" even under the private sphere.

⁶⁶ *Id.*

⁶⁷ *Id.* Which is wise because a badly reasoned constitutional interpretation could be termed judicial 'overreach', lest the courts forget Justice Bhagwati's statement in *D.C. Wadhwa v. State of Bihar*, (1987) 1 SCC 378, where he stated that "[i]t is settled law that a constitutional authority cannot do indirectly what it is not permitted to do directly. If there is a constitutional provision inhibiting the constitutional authority from doing an act, such provision cannot be allowed to be defeated by adoption of any subterfuge."

⁶⁸ See Article 32 (Supreme Court) & Article 226 (High Courts), Constitution of India.

⁶⁹ See National Commission to Review the Working of the Constitution, A consultation paper on: Liability of the State in Tort, (January 8, 2001), available at

<http://lawmin.nic.in/ncrwc/finalreport/v2b1-13.htmv> (last accessed on June 2, 2018)

⁷⁰ And therefore, not private 'individual' interest. See Chapter 3 of this thesis for a discussion on the *Swasthya Adhikar Manch v Union of India*, (*SAM case*).

⁷¹ Article 300, Constitution of India provides for the State to be sued as juristic personality. But for a tortious action brought against the state for the act of its servants, the basic elements that must be

executed entirely by private actors. **(B)** would only be possible in a government-run (or government-sponsored) trial or where an investigator was working in the capacity of an employee of the state. There is much to be discussed here in terms of constitutional theory and practice in India, but for brevity, I will limit the discussion to these particulars, as it is just one of the remedial avenues for claims arising out of lack of informed consent in research. I will now look at the treatment of lack of informed consent under the Human Rights Act, 1993.

4.2.5. Violation of the Human Rights Act, 1993

India passed the Protection of Human Rights Act in 1993. Under this Act, there were provisions to set up the National Human Rights Commission (NHRC) and State Human Rights Commissions (SHRCs) in the states.⁷² The mandate of this Act is extended only to the acts of public servants,⁷³ which means that, as with constitutional law, the ‘verticality’ of rights is observed. Human rights⁷⁴ are therefore enforceable only against the state and private parties are kept outside the purview of this Act.

In 2011, upon receiving complaints by various groups that drug companies were conducting clinical trials of new medicines on the poor without their informed consent, the NHRC issued notices to the Union Health Secretary, ICMR, and DCGI, calling for reports on allegations of fatal drug trials in the country.⁷⁵ It even recommended some guidelines to the Union Secretary of Health on better regulation

present are: a) the employer-employee relationship must be determined, b) the act of the state servant must have been done while carrying out her duties in official capacity, and c) there must be harm caused to the life or property of the claiming individual. *See generally* J. W. Neyers, *A Theory of Vicarious Liability*, ALBERTA LAW REVIEW, Vol. 43, Issue No. 2, (2005).

⁷² Sections 3 and 21, Protection of Human Rights Act, 1993.

⁷³ Section 13, *Id.*

⁷⁴ Section 2(d) of the Human Rights Act, 1993, says ““human rights” means the rights relating to life, liberty, equality and dignity of the individual guaranteed by the Constitution or embodied in the International Covenants and enforceable by courts in India.”

⁷⁵ NHRC Case No. 787/6/0/2011, *see also* NHRC issues notices to the Union Health Secretary, ICMR and DCGI calling for reports on allegations of fatal drug trials in the country, (August 12, 2011), available at

<http://www.nhrc.nic.in/dispArchive.asp?fno=2364> (last accessed on June 2, 2018)

of clinical trials in India.⁷⁶ However, when a petition on the same cause of action was filed in the Supreme Court, the NHRC had to relinquish its authority on the matter, as the Commission cannot inquire into *sub judice* cases.⁷⁷ The role of the NHRC in India is more-or-less a ‘paper tiger’. Its decisions are not legally binding⁷⁸ and it cannot take cognizance of human rights violations if they are reported one year after their occurrence.⁷⁹ It can, however, call for compliance reports and ask the authorities to follow up on them.⁸⁰ Hence, it is quite effective in drawing the government’s attention to rights violations.

Now that we have taken note of the avenues available to individuals under public law, let us consider the remedies available to individuals under private law in India.

4.2.6. Remedy under private law/tort law

Private law is the body of law that deals with horizontal interactions between individuals in their capacities as private actors.⁸¹ It is unclear whether individuals have a private right to action to receive damages for lack of informed consent in clinical research in India. So far, there has not been a single reported case with that cause of action.⁸²

⁷⁶ NHRC sends draft guidelines on clinical drug trials to the Union Health Secretary: Also decides to file an affidavit in the Supreme Court on the issue, (August 20, 2013), available at <http://nhrc.nic.in/dispatchArchive.asp?fno=12968> (last accessed on June 2, 2018)

⁷⁷ Section 36, Protection of Human Rights Act, 1993.

⁷⁸ Under Section 18(b) of the Protection of Human Rights Act, 1993, the NHRC has the right to “approach the Supreme Court or the High Court concerned for such directions, orders or writs as that Court may deem necessary.” Hence, this is one method of making sure that the state authorities comply with the orders of the Commission. High Courts in states like Uttar Pradesh have ruled that the orders of the NHRC are not merely recommendatory in nature and States are duty bound to comply with the orders, and that if they are aggrieved by the order they must seek judicial review, *See State of U.P. v. NHRC, W.P. (Civil), 15570 of 2016*.

⁷⁹ *Supra* note 77.

⁸⁰ *See* Section 18, Protection of Human Rights Act, 1993.

⁸¹ M. Rosenfeld, *Rethinking the Boundaries between Public Law and Private Law for the Twenty First Century: An Introduction*, INTERNATIONAL JOURNAL OF CONSTITUTIONAL LAW, Vol. 11, (2013), p. 126.

⁸² This is the conclusion based on my research conducted on online legal databases and legal resources in the libraries.

Commentators have suggested that there is not much tort litigation in India due to the high costs of litigation.⁸³ It could perhaps be one of the reasons why rights-based avenues (human rights or fundamental rights based) are currently more popular where issues related to clinical trials are concerned in India.⁸⁴ Tort law development has been somewhat patchy in India.⁸⁵ Even though there is a respectable body of case law on medical negligence,⁸⁶ most of it derives from foreign precedents and there is, to my knowledge, no precedent on lack of informed consent in clinical research as the sole cause of action. Therefore, if someone wanted to employ a private law remedy under tort law in India for lack of informed consent in clinical research, the courts would perhaps like to note how the private right to action is invoked in other common law jurisdictions. Let us first find out if such a private right to action for lack of informed consent is recognised in other common law jurisdictions.

4.2.7. Informed Consent in the research context: lessons from other jurisdictions

There has been a steady increase in lawsuits in the USA based on investigators' failure to take informed consent in the United States of America.⁸⁷ Despite such an

⁸³ See K. B. AGRAWAL & V. SINGH, *PRIVATE INTERNATIONAL LAW IN INDIA*, (Kluwer Law International, 2010), p. 135.

⁸⁴ The third chapter traced the Kalpana Mehta and SAM case which are the two major cases on clinical trials filed as PIL in the Indian Supreme Court, thereby showing the extent of rights based claims in this field.

⁸⁵ P. Reddy, *A Small But Significant Victory For Tort Law And Civil Liberties*, LIVE LAW, (October 6, 2017), available at <http://www.livelaw.in/small-significant-victory-tort-law-civil-liberties/> (last accessed on June 2, 2018). In this article, the author while writing a commentary on a rare case specifies why tort law in India has not been fully developed in form and function, says "In India due to the enactment of sector specific legislation we have a splintered system of special fora like the consumer courts or the railways claims tribunal or the motor vehicle claims tribunal that deal with claims that would otherwise be dealt with by civil courts under ordinary tort law", he also raises concerns with the Constitutionalisation of private wrongs and admits how rare it is for people to approach civil courts when their civil rights are infringed by another person or by the government.

⁸⁶ See generally T. K. KOLEY, *MEDICAL NEGLIGENCE AND THE LAW IN INDIA: DUTIES, RESPONSIBILITIES, RIGHTS*, (Oxford University Press, 2010)

⁸⁷ M. M. Mello, et al., *The Rise of Litigation in Human Subjects Research*, ANNALS OF INTERNAL MEDICINE, Vol. 139, (2003), p. 40; A. Dembner, *Lawsuits Target Medical Research-Patient Safeguards, Oversight Key Issues*, BOSTON GLOBE, (August 12, 2002), available at <https://www.sskrplaw.com/lawsuits-target-medical-research-patient-safeguards-oversight-ke.html> (last accessed on June 2, 2018)

increase in lawsuits, scholars claim that the courts have rarely succeeded in extending a right of private action to lack of informed consent in clinical research.⁸⁸ An analysis of case law from the US confirms this claim. For instance, in *Wright v. Fred Hutchinson Cancer Research Center*,⁸⁹ (hereafter *Wright* case) the Cancer Research Center and its investigators were sued by family members of cancer patients who had participated in a series of clinical trials conducted by the Center. The clinical trials used T-cell depletion in an effort to prevent graft-versus-host-disease (GVHD), which is a major cause of death in bone marrow transplant recipients. Several patients, who were enrolled in the trial, died. The patients' families brought the following claims against the Center:

- 1) The federal regulations that defined research requirements for informed consent in clinical trials, known as the Common Rule⁹⁰ had been violated and the families of patients could sue under the Civil Rights Act of 1983.⁹¹
- 2) Since the families of the patients had due process rights as guaranteed under the US Constitution under the 14th Amendment, these rights were violated when the Center interfered⁹² with the Institutional Review Board (IRB) procedures. There were no adequate research procedures in place and the patients had suffered harm because of the Center's negligence in not informing the patients that the GVHD treatment was known to cause bone

⁸⁸ V. G. Koch, (2015), *supra* note 7.

⁸⁹ *Wright v. Fred Hutchinson Cancer Research Center*, 269 F. Supp. 2d 1286 (W.D. Wash. 2002).

⁹⁰ 45 C.F.R. §46 et seq. (2002). The Federal Policy on the Protection of Human Subjects in the US, also called the 'Common Rule', was adopted by federal government agencies to promote uniformity in the conduct of human subjects research. Clinical research in the US is overseen by the Office of Human Research Protections (OHRP), which is an office within US Department of Health. The OHRP ensures regulatory compliance and provides guidance for the conduct of such research.

⁹¹ 42 U.S.C.A. 1983.

⁹² The families alleged that the Center did not disclose relevant information to the Institutional Review Board (IRB) and intimidated the IRB in direct violation of the federal regulations. They also alleged that the investigators had a 'financial interest' for conducting the trial because they owned stock in the company that was responsible for supplying materials for the trial. These claims were based on a report carried by the Seattle times, see D. Wilson & D. Heath, *Patients Never Knew They the Full Danger of Trials They Staked Their Lives on*, SEATTLE TIMES, (2001), available at http://old.seattletimes.com/uninformed_consent/bloodcancer/story1.html (last accessed on June 2, 2018)

marrow rejection. (It is important to note that the plaintiffs did not bring a specific claim against the Center under the tort of negligence.)

- 3) They claimed that since the US had accepted the Nuremberg Code, Declaration of Helsinki, and the Belmont Report,⁹³ it signified that the US accepted the right to be treated with dignity and the right to informed consent as the standard in its due process jurisprudence.

The US District Court for the Western District of Washington dismissed all of the claims made by the patients' family. It granted the Center's motion for judgment in its favour. The jury found that the trial participants had given their consent.⁹⁴ It also found that a reasonably prudent fully informed person in their position would have made the choice to participate in the clinical trial. The court held that breach of informed consent in clinical trials is not deemed a violation of a federal right as defined by law. The court said that:

- 1) There was no statutory basis for the private rights of action that the petitioners sought to assert. It noted that there was no legal support for a private right to action or a civil rights claim because neither statute nor legislation had defined a right of action for a regulatory violation under the Common Rule.
- 2) The 14th Amendment entitles citizens to have adequate due process, which means that the state must have constitutionally adequate procedures to protect

⁹³ The Belmont Report is a concise summary statement of the ethical principles and guidelines for research involving human subjects. The core principles identified in the report were: respect for persons (autonomy), beneficence, and justice, *see* The National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research, The Belmont Report, (1979), available at <https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html> (last accessed on June 2, 2018)

⁹⁴ After due consideration of facts the jury found that the plaintiffs did not prove any missing information that would have changed the patients' decisions. The court held that "[t]he entire complaint is couched in terms of the decedents' 'participation in [the study],' with no indication that such participation was unknowing or that the protocol was anything other than an experiment designed to test new treatments for the type of cancer from which plaintiffs' decedents suffered. Finally, the Complaint acknowledges that plaintiffs' decedents signed 'Consent to Participate' forms which, while not as forthcoming as plaintiffs obviously believe they should have been, informed the participants of both the experimental nature of the protocol and the hoped-for therapeutic results. For all of the foregoing reasons, plaintiffs' motion for reconsideration is DENIED." *supra* note 89, Wright case.

the individuals. But it does not require flawless implementation of these procedures. However, if an imperfect procedure leads to harm, the state must provide an adequate post-deprivation remedy. The court held that the families had access to adequate procedures, like a standard IRB procedure and post-deprivation tort remedies, therefore, the court held that: “defendants' alleged actions in failing to obtain informed consent were random and unauthorized and because there are adequate post-deprivation remedies for their alleged conduct, plaintiffs' Fourteenth Amendment procedural due process rights were not violated”⁹⁵

- 3) The plaintiffs had eventually given up any private right of action under the Nuremberg Code and/or the Declaration of Helsinki. Their claim of a right of action under these documents was later amended to assert that the “precepts set forth in those documents are simply evidence of this country's recognition that certain rights are fundamental under the due process clause of the Fourteenth Amendment.”⁹⁶

If the *Wright* case were to be applied to India, the court could find a similarity in the statutory absence of a right to private action. The Drugs and Cosmetics Act, 1940 does not prescribe any remedial clause for the failure to observe informed consent procedures for clinical trials. Moreover, a potential claim for lack of informed consent leading to violation of a fundamental right guaranteed by the Constitution of India would not stand if an Indian court were to consider what the US court in *Wright* noted:

...defendants' failure to make disclosures necessary to the informed consent process in a therapeutic, experimental setting, does not implicate rights that are so rooted in the tradition and conscience of our people as to be ranked as fundamental. A doctor's tortious failure to obtain informed consent is not a threat to our citizens' enjoyment of ordered liberty, even when the doctor is employed by the state. Although the failure to obtain informed consent necessarily throws some doubt on the voluntariness of the patient's participation in a research study, such a failure does not raise the specter of the type of

⁹⁵ *Supra* note 89. Moreover, the court noted that the “[p]laintiff has not identified, and the Court has not found any case which has equated lack of informed consent in the medical context with a constitutional violation.”

⁹⁶ *Id.*

involuntary, non-therapeutic experimentation which shocked the nation after World War II and gave rise to the Nuremberg Code.⁹⁷

However, there have been cases where courts in the US have held that research participants can bring a claim for lack of informed consent in the research context. But these cases have either involved particular vulnerable population groups (*Grimes* case) or where the investigator has failed to disclose information about the foreseeable risk in research (*Whitlock* case).

The *Grimes v. Kennedy Krieger Institute*⁹⁸ (*Grimes* case) involved non-therapeutic health research on children.⁹⁹ The brief facts of this case are that some researchers from Kennedy Krieger Institute (KKI), an affiliate of the John Hopkins University, conducted a two-year study to measure the usefulness of varying levels of lead abatement procedures in housing. The US Environmental Protection Agency (EPA) and a few local Maryland organizations funded the study. Researchers from KKI were to measure and compare lead dust levels collected in the housing with lead levels in blood samples drawn from children living in those homes over the period of two years.¹⁰⁰ It was necessary to obtain informed consent and parents were notified

⁹⁷ *Supra* note 89.

⁹⁸ *Grimes v. Kennedy Krieger Institute Inc*, 366 Md 29, 782 A2d 807 (2001).

⁹⁹ Paragraphs 12 & 20 of the Declaration of Helsinki, deal with ethical principles related to research on vulnerable individuals and groups who have increased likelihood of being wronged. *See* World Medical Association (WMA), Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects, 1964 (last amended in 2013), available at <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/> (last accessed on June 2, 2018). Part D of the Common Rule has additional protections for trials involving children, *supra* note 90, The Common Rule (2002). India released the ethical guidelines for the biomedical research involving children in 2015. It said that since children usually lack the capacity to consent, the authority to allow the child's participation in a study "rests with parents or guardians, who must provide their permission. However, with respect for children's emerging maturity and independence and investigators must seek to involve children in discussions about research and obtain their assent to participation." It also says that for children, between the ages of 7 and 12 years, oral consent must be obtained from the child in the presence of a parent or legal guardian; for children between the ages of 13 and 18, written consent must be obtained, *See* Indian Council for Medical Research (ICMR), National Ethics Guidelines for Bio-Medical Research involving Children, available at <https://www.nihcollaboratory.org/sites/CbyC/Document%20Library/Draft%20National%20Ethics%20Guidelines%20for%20Biomedical%20Research%20involving%20Children.pdf> (last accessed on June 2, 2018)

¹⁰⁰ The study protocol "required certain classes of homes to have only partial lead paint abatement modifications performed ...[and]...required, the landlords to rent the premises to families with young children.", *Grimes* case, *supra* note 98, pp. 811-812.

of their children's blood levels and the results of the lead dust collection in their homes. The report on blood levels was evidence of the effectiveness of a particular level of abatement. Two families that received less than full lead abatement brought the KKI to court on the grounds that KKI deliberately delayed the reporting of results that would have allowed them to prevent their children from being exposed to high levels of lead, and that KKI inadequately informed them about the hazards and risks involved in the study.

In this case, the trial court ruled in favour for the investigators, but the Maryland Court of Appeals reversed the decision. The Court of Appeals held that the informed consent requirement under the Common Rule created a duty of care that arose out of a “special relationship” between the investigator and research participant and such a breach of such duty was actionable under state law. The court said:

Such research programs normally create special relationships and/or can be of a contractual nature, that create duties. The breaches of such duties may ultimately result in viable negligence actions. Because, at the very least, there are viable and genuine disputes of material fact concerning whether a special relationship, or other relationships arising out of agreements, giving rise to duties existed between KKI and both sets of appellants.¹⁰¹

The court held that the study conducted by KKI lacked full informed consent of participants and the research did not comply with federal regulations.¹⁰² The court reiterated the *Canterbury* principle that the standard for disclosure is whether a reasonably prudent fully informed person would have decided to participate in the research. It then held that the KKI breached the duty of care by not disclosing information that the participant or the participant’s surrogate would have liked to know in terms of the ‘foreseeable risks’ of the study. The decision rested on the fact that the KKI waited nine months to disclose “hot spots” of high lead exposure to parents, even after the child's blood was found to contain elevated levels of lead.

¹⁰¹ *Supra* note 98.

¹⁰² *Id.*, the court also noted, “[t]here clearly was more than a minimal risk involved. Under the regulations, children should not have been used for the purpose of measuring how much lead they would accumulate in their blood while living in partially abated houses to which they were recruited initially or encouraged to remain, because of the study.”

It is important that we analyse this case thoroughly to determine whether this case extends a private right to action in all research-based cases. The court determined that a “special relationship” existed in this case because it involved healthy children who required surrogate consent to participate in the study. Moreover, the research was non-therapeutic (gave no direct benefit to the research participant) and there was more than ‘minor’ risk involved. These factors made the case ‘special’. Furthermore, the court said, “whether a duty of care existed between the parties is a question to be determined by the trier of fact on a case-by-case basis.”¹⁰³ Koch suggests, and I concur, that since no other court in the US has found such a “special relationship” between investigators and research participants, “it would be presumptuous to assume, based on this single court's narrow holding, a general private right of action for participants for failure to disclose the risks and benefits of a research protocol.”¹⁰⁴ I would argue that if such a case were to come before a court in India, it ought to follow a similar ‘case-by-case’ strategy to determine the nature of relationship between the research participant and the researcher.

The other case mentioned above was *Whitlock v. Duke University*,¹⁰⁵ (the *Whitlock* case). In this case, Leonard Whitlock participated in a simulated deep dive experiment to study high-pressure nervous syndrome. During the study, he suffered permanent organic brain damage. Whitlock alleged that Duke University had failed to warn him of the risk of organic brain damage and was, therefore, negligent in its duty to fully inform the participant about the ‘foreseeable risks’. The court held that the degree of required disclosure of risks is higher in the non-therapeutic research context than in the treatment context. The Court did not reach the issue of whether a private cause of action in favour of an experimental subject arises from the Common Rule. It granted a summary judgment¹⁰⁶ to Duke University on the negligence issue

¹⁰³ *Id.* The court referred to the *Williams v. Maynard*, 359 Md. 379, 754 A.2d 379 (2000) where the majority opinion concluded the same.

¹⁰⁴ Koch, (2015), p. 193, *supra* note, 7.

¹⁰⁵ *Whitlock v. Duke University*, 637 F. Supp. 1463 (M.D.N.C. 1986).

¹⁰⁶ The court noted that a “[s]ummary judgment is proper when it appears ‘that there is no genuine issue as to any material fact and that the moving party is entitled to a judgment as a matter of law.’”

as it concluded that no genuine issue of fact exists as to whether the risk of organic brain damage was a ‘foreseeable risk’.

This case is indicative of the legal recognition of a higher degree of disclosure being required for research cases than in treatment. If a case based on a similar cause of action were to arrive before a court in India, the court would have to reconsider its standard opted for disclosure of information.¹⁰⁷ As noted earlier, the *Bolam* test does not do justice to the relationship between a research subject and an investigator. The nature of scientific research into new entities is such that no other investigator would be able to comment on the nature of any other investigator’s research. *Bolam*, in relation to information disclosure, has largely been abandoned in other common law jurisdictions. If a court in India were to use a pre-existing standard for information disclosure from the treatment context for dealing with a case under the research context, it might as well be the *Canterbury* principle. Then, at least, the standard of disclosure would be determined by the yardstick of what a reasonable person in the participant’s position would have liked to know about the experimental procedure.¹⁰⁸

Along the same thread of requiring a nominally higher degree of disclosure needed for research rather than the treatment context, the Canadian Court of Appeal in Saskatchewan in the case *Halushka v. University of Saskatchewan et al.* (1965),¹⁰⁹ (hereafter *Halushka* case) was of the opinion that:

¹⁰⁷ Kohli case, *supra* note 12.

¹⁰⁸ But commentators like Haavi Morreim suggest that none of the legal standards, including the reasonable person and objective standard, for information disclosure seem apt for the research context. He is of the opinion that the research context requires a sharply different approach. “A physician-based standard could expect little or no disclosure, if physicians’ prevailing practice were to conceal information. The “reasonable patient” has little applicability because the decision to enter research is highly individual. Research does not aim to benefit any particular patient, and people can have a wide variety of reasons for entering research, from altruism to financial gain to a desperate, last-ditch hope for cure. The Belmont Report came to the same conclusion back in 1979, finding both the conventional disclosure standards “insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care.” See E. H. Morreim, *Litigation in Clinical Research: Malpractice Doctrines Versus Research Realities*, JOURNAL OF LAW AND MEDICAL ETHICS, Vol. 32, (2004), p. 479; see also The Belmont Report, *supra* note 93.

¹⁰⁹ *Halushka v. University of Saskatchewan et al*, 53 D.L.R. (2d) 436 (Sask. C.A.) (1965).

[T]he duty imposed upon those engaged in medical research...to those who offer themselves as subjects for experimentation, as the respondent did here, is at least as great as, if not greater than, the duty owed by the ordinary physician or surgeon to his patient. There can be no exceptions to the ordinary requirements of disclosure in the case of research as there may well be in ordinary medical practice. The researcher does not have to balance the probable effect of lack of treatment against the risk involved in the treatment itself. The example of risks being properly hidden from a patient when it is important that he should not worry can have no application in the field of research. The subject of medical experimentation is entitled to a full and frank disclosure of all the facts, probabilities and opinions which a reasonable man might be expected to consider before giving his consent.¹¹⁰

This case involved a student who was paid \$50 to participate as a research subject in a test of a new anaesthetic. He was informed that the test involving a “new drug” was “safe” and he had nothing to worry about. He was also not informed that a catheter or a tube would be inserted into his heart; he was allegedly led to believe that the tube would be inserted in his arm. The plaintiff had signed a consent form. During the test, the plaintiff suffered from a cardiac arrest, but he was resuscitated. The plaintiff sued the defendants for trespass to person and negligence. The plaintiff’s claim for both trespass and negligence succeeded at the original trial. He was allowed to recover \$22,500 as damages from the defendants, and the Court of Appeal upheld the verdict for damages but only under trespass, not negligence. While reaching its decision the court noted that in medical cases, an actionable trespass to person is said to have occurred if consent is not informed and freely given. The court also went into the risk versus benefit analysis of the research. It held that since the plaintiff was simply a research subject who received no therapeutic benefit from the research, he was entitled to a complete and frank disclosure of all facts, probabilities, and opinions, which a reasonable person might be expected to consider before consenting to the test.¹¹¹

The Indian court in *Kohli* was not quite clear in making a distinction between the tort of battery and negligence. It appears that the court was open to the idea of determining a liability under either negligence or battery, whichever suited the facts

¹¹⁰ *Id.*, ¶ 29.

¹¹¹ *Id.*, ¶ 29.

of the case more.¹¹² But in *Halushka*, the Canadian court made a distinction between the two torts. It said that the jury could have found that a negligent act on the part of the researchers might have led to trespass to the person, but that did not mean that the action related to the tort of negligence.¹¹³ More significantly, the *Halushka* case considered the differences between the research and treatment context and suggested that the standard of information disclosure under informed consent was a little higher than that required for in treatment. This was because there could be no case for exception to omit information for the welfare of the research participant, like a doctor could for the benefit of the patient. Morreim, while writing about the legal treatment of informed consent in research has written about the need for courts to understand the difference between the two contexts, he writes:

Across this spectrum, the message is not that research injuries are somehow worse (or better) than medical malpractice, or that we need to augment (or diminish) the available causes of action against research errors. The message is simply that research is different, that courts need to be more knowledgeable and to think more clearly if they are to build an adequate foundation by which to guide conduct in this increasingly important realm.¹¹⁴

To sum up the position on lack of informed consent in research, the US courts have recognised a “special relationship” between investigators and research subjects in a case involving children. They have recognised that a higher degree of disclosure is needed in research cases. They have also held that lack of informed consent does not provide a private right of action under federal regulations (Common Rule) and if an alternative remedy exists (as it does in tort); lack of informed consent is not a violation of due process (violation of life and person liberty). The Canadian position is that a higher degree of disclosure is needed for research, especially for non-therapeutic research in which the risk is higher and which is of little benefit to the research subject. It is pertinent to note that each of these cases had different facts and completely different claims, which shows that the right to recover for lack of informed consent in research is not as established as it is under treatment. Moving

¹¹² The court in the Kohli case responded to a question framed as: “Whether the Respondent is guilty of the tortious act of negligence/battery amounting to deficiency in service, and consequently liable to pay damages to the appellant?”

¹¹³ *Id.*, ¶ 37.

¹¹⁴ *Supra* note 108, Morreim, (2004), p. 476.

further, the cases that I have mentioned so far dealt with inadequate consent in the research context. I will now look at a case where the court had to deal with complete lack of consent, i.e., non-consensual cases of clinical research.

4.2.8. Non-consensual research

In the case of *Mink et al. v. University of Chicago*,¹¹⁵ the plaintiff along with a thousand other women was given diethylstilbestrol (DES) as part of a double blind study to study the affect of DES on preventing miscarriages. The plaintiffs were neither told that they were to be a part of an experiment nor were they told that they were being given DES, as such they alleged that their newly born daughters developed cervical abnormalities and that led to an increased risk of cancer in them and their daughters. The court held that the cause of action that could succeed was of battery since there was a complete lack of informed consent as the case involved “unauthorised touching” without the consent of the person. This equated to the tort of battery. Here again, as in *Halushka*, the court differentiated between the torts of battery and negligence. The court said that:

While early cases treated lack of informed consent as vitiating the consent to treatment so there was liability for battery, the modern view [quoting from Prosser’s text on torts] “is that the action...is in reality one for negligence in failing to conform to the proper standard, to be determined on the basis of expert testimony as to what disclosure should be made.” Nonetheless, a battery action may still be appropriate in certain circumstances. *Where the patient has not consented to the treatment*, it is meaningless to ask whether the doctor should have revealed certain risks necessary to make the consent an “informed” one.¹¹⁶ [My emphasis]

Summarising the previous two sub-sections, a court in India would have the option to entertain a claim arising out of lack of informed consent in research under the torts of battery or negligence (depending on the facts of the case). As for a private right to action for lack of informed consent in research, whether arising from a statute or other regulatory provision in India, the court would have a difficult time finding one. If a claim under lack of informed consent is filed in the higher courts as a violation of a fundamental right, it will remain at the discretion of the court to determine whether

¹¹⁵ *Mink v. University of Chicago*, 460 F.Supp. 713 (1978).

¹¹⁶ *Id.*

the lack of informed consent amounted to a violation of the right to life and/or personal liberty (a position rejected by the US court in *Wright*).

Having outlined the position of the Indian courts on informed consent and suggesting the lessons that they could learn from other jurisdictions, simply focusing on law in this area is unlikely solve the problems with the *process* of informed consent. Of course, development of a clear and concise legal remedy is required to tackle grievances arising out of a lack of informed consent in research, but there are some limitations that need to be accounted for in any discussion on legal remedies. The next part will draw out some of these limitations.

Part 3. The limits of law

The law of informed consent in research, as described in Parts 1 and 2 above, sets legal standards for information disclosure but does not provide clarity on the redress mechanisms available if the standards are not met. But this is not the only limit of the law of informed consent. In what follows, I will outline a few other limitations of the law.

4.3. Legalism and its pitfalls

As noted in the previous chapter, the law of informed consent has been criticised for having a vision that is subpar to the ethical vision of informed consent.¹¹⁷ A number of commentators have challenged the legal implementation of the principle. One of the strongest criticisms came from Jay Katz, who called the law's vision of informed consent a 'fairy tale' because it "reduces complex human encounters to enchanting simplicity".¹¹⁸

Academics and medical lawyers have commented on how the importance placed on law¹¹⁹ sometimes makes the complexities of moral dilemmas disappear.¹²⁰ This is particularly evident when there are lawyers on ethics committees reviewing

¹¹⁷ J. Katz, *Informed Consent – a Fairy Tale? – Law's Vision*, UNIVERSITY OF PITTSBURGH LAW REVIEW, Vol.39, No. 137, (1977).

¹¹⁸ *Id.*

¹¹⁹ Also referred to as the "law as ethics approach".

¹²⁰ D. K. Sokol, "What does the Law Say?", BRITISH MEDICAL JOURNAL, Vol. 337, Issue No. 7660, (2008);

medical cases or study designs. For instance, Cohen and colleagues while sharing their experiences on ethics committees, noted:

[i]n all cases where there has been a lawyer on the ethics committee; that is, what tends to happen a lot is that everybody looks to one end of the table where the lawyer sits and asks, “What is the answer?” or “Is that legal?” and the lawyer says, “Yes, it's legal, it's fine,” or “No, it isn't.” That, in some cases, will end the discussion.¹²¹

Such a situation depicts the drawbacks of ‘legalism’, which Callahan describes as “the translation of moral problems into legal problems.”¹²² Legalism is characterised by the elevation of the moral judgments of the courts as the moral standards of the land.¹²³ The problem with legalism is that it reduces ethics committees to little more than legal watchdogs who care only about adherence to law, thereby reducing moral reasoning to mere ‘rule-following’.¹²⁴ Such rule-following behaviour also adds to the discrepancy in the theory and practice of informed consent. As noted earlier, law only provides for the bare minimum of acceptable behaviour. However, for meeting the goals of informed consent, practitioners ought to strive for higher standards than the bare minimum. This is essential to ensuring that informed consent is not reduced to a mere tick-box exercise.

It is pertinent to note that the only normative standard that case law has been interested in setting has been the standard for information disclosure. The ideal ethical standard is the subjective standard,¹²⁵ which no leading common law jurisdiction (discounting a state in the USA)¹²⁶ has applied. As for the requirement for ensuring capacity to consent, as noted earlier, India does not have a law

¹²¹ M. Cohen, et al., *Everything You Always Wanted To Ask A Lawyer About Ethics Committees*, CAMBRIDGE QUARTERLY OF HEALTHCARE ETHICS, Vol. 1, (1992), pp. 33-39.

¹²² D. Callahan, *Escaping From Legalism: is it possible?*, HASTINGS CENTER REPORT, Vol. 26, (1996), pp. 34-35.

¹²³ *Id.*

¹²⁴ R. F. Weir, *Paediatric Ethics Committees: Ethical Advisers Or Legal Watchdogs?* LAW, MEDICINE & HEALTH CARE, Vol.15, (1987), pp. 99–110.

¹²⁵ V. Dranseika, et al., *Relevant Information and Informed Consent in Research: In Defense of the Subjective Standard of Disclosure*, SCIENCE AND ENGINEERING ETHICS, Vol. 23, Issue No. 1, (2017).

¹²⁶ The Oklahoma Supreme Court adopted the subjective standard to information disclosure for informed consent in the case *Scott v. Bradford*, 606 P.2d 554 (Okla.1979). *See also*, K. Ivy, *Medical Malpractice: A Subjective Approach to Informed Consent in Oklahoma*, TULSA LAW JOURNAL, Vol. 15, (2013).

equivalent to MCA in the UK. The legal standard for what informed consent should look like in clinical research is not established yet and it echoes the doctrine developed in the treatment context, which I have established, is a different context and creates different relationships. The law heavily borrows from the ethical guidelines but falls short on setting standards to guide the process of informed consent. This is because most questions involved in the *process* of informed consent are essentially moral questions. They require ethical decisions, like does poverty affect a participant's voluntariness to consent, or how much money, or what incentives, must be offered to participants without leading to undue inducement? Is it autonomy enhancing to have to gain the permission of a woman's husband when she says that she would not consent without her husband's permission, and so on. Practitioners face such questions in their day-to-day research work during the process of informed consent. Law does not provide answers to these, but ethical discussions and guidelines do. Therefore, while law helps in post-process situations in determining when consent has been breached, it provides little guidance to the researchers on how to deal with ethical dilemmas during the consent procedure.

For these reasons, in every ethico-legal analysis of informed consent, law seems to fall behind on the ethical requirements for informed consent.¹²⁷ Nevertheless, law, owing to its remedial nature, is more solution-oriented than the slightly more abstract ethics. Faden and Beauchamp, however, note that though ethics might not supply mechanical solutions or definitive procedures for decision-making, they provide a reasoned and systematic approach to moral problems. They write that:

Moral dilemmas require a balancing of competing claims in untidy circumstances, and moral philosophy can make a significant if not decisive contribution. In these respects philosophy is neither surpassed by, nor superior to legal reasoning and legal solutions.¹²⁸

Ethical analysis employs a nuanced and sensitive approach to certain situations that law can sometimes be too blunt to appreciate. De Ville explains this further by

¹²⁷ A. J. Weisbard, *Informed Consent: The Law's Uneasy Compromise with Ethical Theory*, NEBRASKA LAW REVIEW, Vol. 65, (1986).

¹²⁸ R. R. FADEN & T. L. BEAUCHAMP, *A HISTORY AND THEORY OF INFORMED CONSENT*, (New York: Oxford University Press: 1986), p. 19-20.

noting, “in the interest of objectivity and consistency, the legal process, training, doctrine, and tradition have tended to downplay humanity and individuality.”¹²⁹ A case in point is of conjoined twins, the surgical separation of which involved the survival of one at the cost of the other’s life.¹³⁰ While adjudicating in favour of separation, Justice Alan Ward of the English Court of Appeal famously remarked, “this is a court of law, not of morals.”

The purpose of introducing the reader to the drawback of legalism is not to downgrade the importance of law or the legal doctrine. It is to show the distinctness in the legal and ethical underpinnings of informed consent and to advise readers against conflating the two. The other limitation of law is more context specific as will be discussed below.

4.3.1. Limits of law of informed consent in India

We have already seen that claiming a lack of informed consent as a violation of a fundamental right is not as easy as it sounds in principle.¹³¹ We have also seen that

¹²⁹ K. De Ville, “*What does the law say?*” *Law, Ethics, and Medical Decision Making*, THE JOURNAL OF WESTERN MEDICINE, Vol. 160, Issue No. 5, (1994), pp. 478-880. Although this is not the case with all the judges, particularly not when we compare different jurisdictions, and it should not be seen as an all-pervading aspect of judicial decision making. *See also* R. A. Posner, *Realism about Judges*, NORTHWESTERN UNIVERSITY LAW REVIEW, Vol. 105, Issue No. 2, (2011). Additionally, for a commentary on how law’s treatment of decisions requiring ethical engagement is not of the highest calibre, *see* C. Foster & J. Miola, *Who’s In Charge? The Relationship between Medical Law, Medical Ethics, and Medical Morality*, MEDICAL LAW REVIEW, Vol. 23, Issue No. 4, (2015), pp. 505-530.

¹³⁰ *Re: A (conjoined twins)* [2001] 2 WLR 480. Mary and Jodie were conjoined twins who were joined in a manner that Mary, with a primitive brain and weaker structure, was completely dependent on Jodie for her survival. Medical evidence suggested that if the twins lived the same way for long, Mary would be too much of a burden on Jodie and neither child would survive. However, if they were to be surgically separated, Jodie would have a stronger chance of survival than if nothing was done, but separation would mean the certain death of Mary. The parents of the twins were against the separation. The doctors applied to the court for a declaration that it would be lawful and in the best children of the children to operate. The UK High Court granted the declaration analogising the case with that of the withdrawal of life support. The parents appealed against the declaration. The Court of Appeal dismissed the application, each judge preferring their own reasons for the dismissal. The case caused intense debate for its heavy moral overlay as the court had to consider whether one child could be sacrificed in order to save the other, and why such a conclusion was not an unlawful killing.

¹³¹ *Supra* notes 64 and 65 (for Constitutional Law in India). *See also* the court’s statement in the Wright case (US), “[a]lthough the failure to obtain informed consent necessarily throws some doubt on the voluntariness of the patient’s participation in a research study, such a failure does not raise the specter of the type of involuntary, non-therapeutic experimentation which shocked the nation after World War II and gave rise to the Nuremberg Code”, *supra* note 89.

there is no option to claim lack of informed consent as a statutory right. Therefore, the focus here will be on tort law. But before I address the limitations of tort law that are specific to India, I want to first address the general limitation of tort law in dealing with the lack of informed consent in research.

It is generally accepted that the legally recognised right to informed consent is aimed at protecting the autonomy of the research participant. But commentators question the sufficiency of the present legal doctrine with regards to protection of autonomy. Morreim, for example, is of the opinion that the standard legal doctrine of informed consent does not sufficiently protect autonomy where there is no demonstrable physical harm to the individual. He writes:

[B]ecause standard informed consent doctrine usually limits recovery to cases featuring a physical or other separate injury, it can fail to honor human autonomy in cases where someone's right to choose has been abused without demonstrable physical damage. If this is a problem in ordinary medicine, it is even more so in the research setting.¹³²

I do not think that this criticism is sound to the extent that there are claims that can succeed under the tort of battery without a demonstrable physical damage.¹³³ Moreover, even though it is rare and often difficult to claim, people with no physical injury after having proven 'infliction of emotional distress' have also been able to recover damages under tort law.¹³⁴ Serious dignitary harms¹³⁵ can also be rectified

¹³² Morreim (2004), *supra* note 108.

¹³³ See generally A. BEST, ET AL, BASIC TORT LAW: CASE, STATUTES AND PROBLEMS, (4th edn, Kluwer Law and Business, 2014)

¹³⁴ Lack of informed consent in research could potentially to emotional distress. Intentional Infliction of Emotional Distress (IIED) tort is an example of the strength of tort law as it shows flexibility to accommodate other forms of 'harm'. See further for an analysis and development of tort law in the area of 'emotional distress', J. L. Kircher, *The Four Faces of Tort Law: Liability For Emotional Harm*, MARQUETTE LAW REVIEW, Vol. 90, Issue No. 4, (2007); see also *Boyles v. Kerr*, 855 S.W.2d 593 (1993), where a girl was surreptitiously videotaped having sexual intercourse by the defendant and his friends; she successfully recovered damages under negligent infliction of emotional distress (NIED).

¹³⁵ Dignitary harms are harms that have been "caused by conduct that overrides patients' autonomy, treats them as less than human, and denigrates them as human beings." See D. S. Davis, *The Ambiguous Effects of Tort Law on Bioethics: The Case of Doctor-Patient Communications*, CLINICAL ETHICS, Vol. 21, (2010), p. 265, such a dignitary harm will most certainly be redressible under the Constitution of India under Article 21, protection of life and liberty. The degree of erosion of autonomy matters and 'treatment of a human as less than human' is a higher degree of violation of

under constitutional rights. Yet some commentators have demanded a new dignitary tort for lack of informed consent in research.¹³⁶ While the right to recover damages under lack of informed consent in research is not as established as the right to recover under treatment; and there is a need for clarity in law pertaining to the treatment of lack of informed consent in research, there is arguably enough flexibility under tort law to address the different nature of the investigator-subject relationships.¹³⁷ An example of this sort of flexibility is the *Grimes* case, in which the court acknowledged the wide knowledge gap between investigators and research subjects and found a “misalignment of interests”.¹³⁸

Yet there are some limitations of tort law that are specific to India. On problems facing the law of torts in India, Thanvi writes:

The received English law, and more especially law of torts, has not fared well with the Indian conditions of life, and as such it has not been able to sent [sic] its roots deep into the recesses of the Indian soil.¹³⁹

There is not much reliable data to suggest how much litigation has occurred under tort law as cases in trial courts generally go unreported. Even in the higher courts, only those cases that are marked “fit for reporting” by the judges in the High Courts and the Supreme Court are reported.¹⁴⁰ But from a cursory glance at reported cases, it

autonomy. A right to live a life with dignity has been endorsed by the Indian Supreme Court in the case *Francis Coralie Mullin v. Administrator, Union Territory of Delhi and others*, (1981) 1 SCC 608.

¹³⁶ A. Meisel, *A Dignitary Tort' as a Bridge Between the Idea of Informed Consent and the Law of Informed Consent*, JOURNAL OF LAW, MEDICINE AND ETHICS, Vol.16, Issue 3-4 (1988); A. Weisbard, *Informed Consent: The Law's Uneasy Compromise with Ethical Theory*, NEBRASKA LAW REVIEW, Vol. 65, (1986), p. 763; E. H. Morreim, *In Medical Research Litigation and Malpractice Tort Doctrines: Courts on a Learning Curve*, HOUSTON JOURNAL OF HEALTH LAW AND POLICY, Vol. 4, (2003),

¹³⁷ As a side note, such relationship does not have to be a medical negligence claim. It could be covered under general professional negligence. If a duty of care can be established in such a relationship as per the Caparo test laid out by the UK House of Lords following the case *Caparo Industries PLC v. Dickman*, [1990] UKHL 2, then liability could be imposed on investigators and perhaps even on research sponsors.

¹³⁸ S. A. Alessi, *The Return of Results in Genetic Testing: Who Owes What to Whom, When, and Why?*, HASTINGS LAW JOURNAL, Vol. 64, (2013), p. 1715; *Grimes* case, *supra* note 98.

¹³⁹ S. C. Thanvi, *Law of Torts*, in: J. MINATTUR (ED.), THE INDIAN LEGAL SYSTEM, (2nd edn., Indian Law Institute, 2006), p. 668-671

¹⁴⁰ Generally it is only the cases that appear before High Courts, Supreme Courts, Labour Tribunal, Company Law Appellate Tribunal, Consumer Disputes Redressal Fora, and some other judicial and

is evident that litigation under tort law is sparse when compared to other common law jurisdictions. Marc Galanter conducted a ten-year survey (1975-1984) on tort litigation in India and concluded that tort law in India was unsystematic, largely neglected, and infrequently resorted to by the people.¹⁴¹ Noting the poor development of tort law in India, Cassels also remarked that, “[a]t least until now the law of tort in India is little more than a myth about how people would be cared for in a better world.”¹⁴² While the works cited rely on data from decades ago, little seems to have changed to undermine their findings.¹⁴³ These works were one of the few exhaustive academic commentaries on the status of tort law in India, suggesting in addition that not much academic attention has been paid to it.

Nevertheless, a significant portion of the criticism directed against tort law in India is procedural and logistical. There is a long-standing problem of paucity of judges in India,¹⁴⁴ but more importantly, there is a lack of specialisation amongst lawyers. As Galanter, based on his years of research conducted on tort law in India, noted “[o]ne may visualize Indian lawyers as stuck in a hyper-individualized bazaar economy in which virtually all lawyers offer the same narrow range of services.”¹⁴⁵ This remark was made three decades ago, but even today, with the advent of many professional and large scale law firms, tort law as a specialisation has not seen much development. Considering the fact that Indian lawyers work with little to no institutional support for specialised knowledge, with no specialist organisation or specialised technical publication in tort law, and coupled with the recent trend of

quasi-judicial bodies that get reported, but not tort cases that appear before lower courts, *See* S. K. Bhatia, *Specific Problems of Torts Law in India*, JOURNAL OF THE INDIAN LAW INSTITUTE, Vol. 11, Issue No. 4, (1969).

¹⁴¹ M. Galanter, *When Legal Worlds Collide: Reflections on Bhopal, the Good Lawyer, and the American Law School*, JOURNAL OF LEGAL EDUCATION, Vol. 36, Issue No. 3 (1986), pp. 292-310, p. 296.

¹⁴² J. CASSELS, *THE UNCERTAIN PROMISE OF LAW: LESSONS FROM BHOPAL*, (University of Toronto Press, 1996), p. 153.

¹⁴³ *Supra* note 85, Reddy (2017).

¹⁴⁴ *See generally* A. Mathur, *State on Indian judiciary report: ‘Lack of judges, inefficient management behind delays’*, THE INDIAN EXPRESS, (August 11, 2016), available at <http://indianexpress.com/article/india/india-news-india/judges-shortage-pending-cases-inefficient-management-2967172/> (last accessed on June 2, 2018)

¹⁴⁵ Galanter (1986), *supra* note 141, p. 297.

constitutionalising private law,¹⁴⁶ Galanter's reasonable critique from 1986, that tort law in India is unsystematic and largely neglected, still holds. There are also significant barriers to access like lack of legal aid, high court fee, and lack of insurance to cover legal fee. These barriers, along with the protracted delays and meagre recoveries, have made people wary of litigation in India. A combination of all these factors has contributed to the underdevelopment of tort law in India.

Despite all these drawbacks, it is nonetheless possible that the courts in India adopt an innovative application of tort law¹⁴⁷ if presented with the right opportunity and a rightly argued case. As Basu fittingly notes:

It seems that the problems of tort law in India lie not so much in the laws themselves as in their use and application. As such they may have much to do with economic and political realities of a more general "underdevelopment" in a Third World nation. After all the number of judges and courts available is really a product of economic necessities and political choices.¹⁴⁸

These logistical problems aside, there is reason to believe that the Indian courts will forego their current approach to informed consent under tort law and adopt a modern approach to cases dealing with lack of informed consent. The source of this optimism lies in a recent statement pronounced by a two-judge bench of the Supreme Court that said "[i]n the times to come, litigation may be based on the theory of lack of informed consent."¹⁴⁹

¹⁴⁶ S. Balganes, *The Constitutionalization of Indian Private Law*, PENN LAW FACULTY SCHOLARSHIP PAPER, 1557, (2016). In this piece the author notes the recent trend of hybridisation of public and private law in India. Here a private law claim is brought as a public law action against a state actor rather than as a private action against a private actor – which despite giving short-term benefits to litigants has added to the ailing private law apparatus, especially that of tort law in the country.

¹⁴⁷ Much like their innovation and legal creativity in galvanising law for the poor, *See generally* J. Cassels, *Judicial Activism and Public Interest Litigation in India*, AMERICAN JOURNAL OF COMPARATIVE LAW, Vol. 37, Issue no.3, (1989), pp. 495-519.

¹⁴⁸ A. Basu, *Torts in India: Dharmic Resignation, Colonial Subjugation, or "Underdevelopment"?*, THE SOUTH ATLANTIC QUARTERLY, Vol. 100, Issue No. 4, (2001), pp. 1053-1070.

¹⁴⁹ *Malay Kumar Ganguly v. Sukumar Mukherjee & Ors*, (2009) 9 SCC 21, the Court held that "medical negligence cannot be attributed for not rendering a facility which was not available", it also made an observation (without referring to Samira Kohli) that with changing times the "[d]octors increasingly must engage with patients during treatments especially when the line of treatment is a contested one and hazards are involved. Standard of care in such cases will involve the duty to disclose to patients about the risks of serious side effects or about alternative treatments."

4.4. Conclusion: Need for Empirical Data

The legal doctrine of informed consent focuses on the post-fact and post-injury aspect of informed consent. The focus on the *process* of consent is only as much as is needed to determine liability. This chapter has tried to demonstrate what happens (or could happen) when actions leading to informed consent come to rest within the ambit of law. There is an enormous difference between the *material facts* of a case that a court would consider worthy of consideration and the *social facts* that determine the actual process of consent. This difference also contributes to the theoretical-practical divide in the larger conversation on informed consent.

This chapter makes it evident that individual cases claiming a lack of informed consent in research do not often reach a court of law, and in India's case, they have not reached the court at all. But it would be naïve to deny the significant effect that law has on the whole process of informed consent. People take and give consent in the shadow of law. By better understanding how stakeholders understand the role of law in informed consent, it may be possible to find newer ways within the law, and outside of it, to improve the informed consent process. Mnookin and Kornhauser write:

Theoretical and empirical research concerning how people bargain in the shadow of law should provide us with a richer understanding of how the legal system affects behaviour, and should allow a more realistic appraisal of the consequences of reform proposal.¹⁵⁰

Therefore, a few questions need further probing. These questions include: what do the authorities and stakeholders involved in the process of informed consent think about the role of law? Do the stakeholders involved in clinical trials perceive informed consent as an ethical obligation or a legal compulsion? Is legalism prevalent within the clinical research spectrum in India? These questions are empirical in nature and require a different approach than the one taken here thus far. Answers to these questions will provide a window into the actual practice and process of informed consent and will give a grounded perspective to the more

¹⁵⁰ R. H. Mnookin & L. Kornhauser, *Bargaining in the Shadow of the Law: The Case of Divorce*, THE YALE LAW JOURNAL, Vol. 88, Issue No. 5, (1979), pp. 950-997.

abstract discussions already elaborated. Most of the information collected in the chapters so far has been obtained through documentary review. But when considering empirical questions we must remember Atkinson and Coffey's advice to researchers to carefully use document review as a method of data collection. They write:

[w]e should not use documentary sources as surrogates for other kinds of data. We cannot, for instance, learn through records alone how an organization actually operates day-by-day. Equally, we cannot treat records - however 'official'- as firm evidence of what they report... [this kind of] strong reservation does not mean that we should ignore or downgrade documentary data. On the contrary, our recognition of their existence as social facts alerts us to the necessity to treat them very seriously indeed. We have to approach them for what they are and what they are used to accomplish.¹⁵¹

Hence, to arrive at a more realistic depiction of the principle of informed consent as applicable to human subject research in India, I will be employing social science research methods for data collection. The next chapter will outline the qualitative methodology in trying to gauge various stakeholders' view on informed consent in research. The stakeholders' views shed a light on the reasons participants are encouraged to volunteer for clinical research. They also shed light on what practitioners think about informed consent, in other words, what motivates them to take informed consent from the participants. Once we understand their motivations, it will be easier to comprehend the reasons why informed consent procedures have taken their present form in India.

¹⁵¹ P. A. Atkinson & A. Coffey, *Analysing documentary realities*, In: D. SILVERMAN (ED.), *QUALITATIVE RESEARCH: THEORY, METHOD AND PRACTICE*, (Sage Publishing, 1997), p. 47.

RESEARCH METHODOLOGY

5.0. Introduction

The focus will now shift to the methodological approach adopted by this thesis in order to answer the empirical question: *How is the principle of informed consent perceived by the different stakeholders involved in the process of informed consent in clinical research in India?* We have already seen how the ethical and legal approaches to informed consent interact with each other in the previous chapters. To understand how these two approaches interact with the practice of informed consent, we will look at how the principle of informed consent is perceived by the different stakeholders involved in the process of informed consent in clinical research in India. By ‘different stakeholders’ I mean people who fall within the spectrum of clinical research in India and have a say in how informed consent plays out in practice. Therefore, along with the influence of the grounded theory methodology (described below), I employ a multi-stakeholder approach to data collection and a contrasting method to analyse the data in order to grasp the bigger picture of informed consent *in action* as opposed to *in the books*.

5.1. Why the grounded theory methodology?

For any socio-legal study, it is essential to map out the law as it stands, as it is doctrinally understood, and then delve into further exploration of how social actors engage with it.¹ Therefore, along with a desk-based analytical research, that maps the world of law and the theory of informed consent, this research is guided by a qualitative approach that involves inductive reasoning to observe patterns in interview data and reach conclusions. This qualitative approach goes by the name grounded theory.

Grounded theory developed in the field of health and nursing in the United States in the 1960’s. It was developed by two sociologists, Barney Glaser and

¹ See R. BANAKAR & M. TRAVERS (EDS.), *THEORY AND METHOD IN SOCIO-LEGAL RESEARCH*, (Oxford: Hart Publishing, 2005), p.vi.

Anselm Strauss, as a constant comparative method of inquiry.² It is the “actual production of meanings and concepts used by social actors in real settings”.³ It places emphasis on two fundamental points: i) the participant’s own understanding of their social environment is the key for any qualitative inquiry, and ii) the importance for researchers to be creative and flexible to mould their approach to their respective research settings.⁴ This theory was developed as a release-valve from the trappings of *a priori* research, to move beyond doctrinal arguments, normative (value) judgments and ideological positions, which are not grounded in empirical data.⁵

Since the theory aims at ‘grounding’ theory in data, it uses a judicious mix of inductive and deductive reasoning.⁶ Inductive reasoning, also called the ‘bottom-up’ approach to research, is where the researcher “uses observations to build an abstraction or to describe a picture of the phenomenon that is being studied”.⁷ It was imperative to take a bottom-up approach in trying to fully address the purpose of the research project, which was to understand the dynamics and the process through which the legal and ethical principle of informed consent is operationalised within the paradigm of biomedical research in India. My research adopted this approach by not just stating what individuals and institutional actors said about informed consent, but also by observing how and within what context they said it.

Strauss and Corbin, the proponents of modern grounded theory approach as

² B. GLASER & A. L. STRAUSS, *THE DISCOVERY OF GROUNDED THEORY: STRATEGIES FOR QUALITATIVE RESEARCH*, (Hawthorne NY: Aldine de Gruyter, 1967). Even though I cite Glaser as Strauss’ work in the main text as the proponents of this methodology I have employed the practical tools to skeletally employ some tools of grounded theory in this project that were outlined by Charmaz in: K. CHAMAZ, *CONSTRUCTING GROUNDED THEORY: A PRACTICAL GUIDE*, (Sage Publications, 2006).

³ R. P. Gephart, *Qualitative research and the Academy of Management Journal*, *ACADEMY OF MANAGEMENT JOURNAL*, Vol. 47, (2004), pp. 454-462.

⁴ D. Francis, *Book Review of Strauss and Corbin’s Basics of Qualitative Research*, *SOCIOLOGICAL RESEARCH ONLINE*, (1999).

⁵ BANAKAR & TRAVERS (2005), p. xlv, *supra* note 1,

⁶ The book ‘Pursuing Grounded Theory in Law’ has guided this research. See A. HELLUM, ET AL., *PURSuing GROUNDED THEORY IN LAW: SOUTH-NORTH EXPERIENCES IN DEVELOPING WOMEN’S LAW*, (Mond Books, 1998). Grounded theory as propounded by Glaser and Strauss also aims at ‘grounding’ theory in data by using an efficient mix of inductive and deductive reasoning. See A. L. STRAUSS & J. CORBIN, *BASICS OF QUALITATIVE RESEARCH TECHNIQUES AND PROCEDURES FOR DEVELOPING GROUNDED THEORY*, (2nd edn., Sage Publications: London, 1998), p. 2.

⁷ M. G. LODICO, ET AL, *METHODS IN EDUCATIONAL RESEARCH: FROM THEORY TO PRACTICE*, (2nd edn., Jossey-Bass, 2010), p. 10.

means of qualitative study, noted that “[i]f someone wanted to know whether one drug [was] more effective than another, then a double blind clinical trial would be more appropriate than grounded theory study. However, if someone wanted to know what it was like to be a participant in a drug study...then he or she might sensibly engage in a grounded theory project or some other type of qualitative study.”⁸ The choice of grounded theory for collecting and coding the data was apt for this project because I was looking at questions like: what does informed consent mean to different stakeholders; how do they understand the intrinsic value of the principle; does law or do ethics prompt them to follow the principle; and what factors, including deficiencies or limitations, determine how they implement the principle? These questions were important to have an understanding of what the principle means to the beneficiaries and bearers, because unless we collect and build upon this knowledge the principle will continue to remain detached from reality.

Any area where health, healthcare, law, economy, politics, and ethics intersect is bound to be a disputed area. The principle of informed consent operates within complex layers of legal, regulatory, administrative, and personal structures. These structures need to be studied in isolation and as part of a bigger picture in order to uncover the many ‘myths’ about the principle of informed consent.⁹ There have been arguments for and against considering the principle of informed consent as ‘fiction’ or a ‘myth’.¹⁰ This thesis intends to highlight that most of these arguments

⁸ STRAUSS & CORBIN (1998), p. 40, *supra* note 6.

⁹ See A. Meisel & M. Kuczewsk, *Legal and Ethical Myths About Informed Consent*, ARCHIVES OF INTERNAL MEDICINE, Vol. 156, Issue No. 22, (December, 1996) pp. 2521-2526; D. Leeb, D. G. Bowers DG & J. B. Lynch, *Observations on the myth of informed consent*, PLASTIC AND RECONSTRUCTIVE SURGERY, Vol. 58, (1976), pp. 280 – 282.

¹⁰ See (for arguments in favour of ‘informed consent’ as legal fiction) M. Epstein, *Why effective consent presupposes autonomous authorisation: a counterorthodox argument*, JOURNAL OF MEDICAL ETHICS, Vol. 32, (2006), pp. 342-345; E. G. Laforet, *The Fiction of Informed Consent*, THE JOURNAL OF AMERICAN MEDICAL ASSOCIATION, Vol. 235, Issue No. 15, (1976), pp. 1579-1585; Faden & Beauchamp write that informed consent is not a legal fiction as it does not presuppose autonomous authorisation, See R. R. FADEN, TOM L. BEAUCHAMP & NANCY M.P. KING, A HISTORY AND THEORY OF INFORMED CONSENT, (New York, Oxford University Press, 1986), pp. 274-297. See also J. Dyckman, *The Myth of Informed Consent: An Analysis of the Doctrine of Informed Consent and Its (Mis)Application in HIV Experiments on Pregnant Women in Developing Countries*, COLUMBIA JOURNAL OF GENDER AND LAW, Vol. 9, Issue No. 1, (1999); W. A. Silverman, *The myth of informed consent: in daily practice and in clinical trials*, JOURNAL OF MEDICAL ETHICS, Vol. 15, (1989), pp. 6-11.

are sometimes at odds with social and institutional reality.¹¹ For understanding the institutional reality, it was important that my interviewees included people who were in authoritative positions and who have a say in validating informed consent procedures to clear the trials. This was in addition to having research participants and investigators as interviewees.

In a strictly doctrinal research, I would not have had the opportunity to conduct an empirical investigation; the focus would have remained on the analysis and manipulation of theoretical concepts. This thesis aimed at exploring the world beyond those theoretical concepts. I tried to push the envelope a little further to understand how the theory of informed consent plays out in a real-life setting. In the grounded theory approach, theoretical development and pattern observation is a continuous iterative process;¹² therefore, interviews conducted under this methodology were more open-ended and interactive in the form of a ‘dialogue’ or ‘discussion’ rather than a ‘question-answer based pattern’. Such an approach enabled most interviewees to relax and give unmanufactured responses.

Additionally, it is important to note that this thesis merely employs a skeletal framework of grounded theory and is restricted to the design of empirical research. I would refrain from calling this thesis a grounded theory project as only some aspects of data collection and coding were guided by the methodology. The data analysis is not guided by this methodology and employs a contrasting method instead which shall be discussed later in this chapter.

The institutional process of informed consent within the context of clinical trials in India has not been documented through such multi-method research before. There is a gap in literature pertaining to the actual process of realising informed consent and the practitioners’ perceptions on the principle.¹³ The tools from the

¹¹ See generally E. LAGERSPETZ, H. IKÄHEIMO & J. KOTKAVIRTA, ON THE NATURE OF SOCIAL AND INSTITUTIONAL REALITY, (SoPhi Academic Press, Finland, 2001).

¹² Iterative process involves continuous rounds of analysis to generate a particular conclusion or sequence explaining a phenomenon.

¹³ There have been qualitative surveys done on ethics of clinical research in India that classified which ethical concerns have been the most pressing, informed consent tops the chart. Also, the role of Institutional Ethics Committees (IEC’s) in the consent screening process has been studied qualitatively which highlight the struggles faced by the IEC’s in India. See M. Jadhav & A. Bhatt,

grounded theory methodology used in designing this qualitative research gave me flexibility to collect the data without worrying about proving a pre-existing hypothesis. It helped me create a hypothesis from the themes that were teased out from the data that was collected during the fieldwork. Furthermore, the flexibilities built into the grounded theory methodology helped me accommodate a multi-stakeholder approach to data collection; details of this approach to data collection that is discussed below.

5.1.1. Multi-stakeholder approach

I chose a multi-stakeholder approach to get a comprehensive picture of the operationalisation and perception of the principle of informed consent. This meant that no stakeholder was given primacy while collecting data, and views and opinions of all the stakeholders were significant. This was one way to understand the perceptions of all the sides involved. As stated above, the principle of informed consent operates within complex layers of legal, regulatory, administrative, and personal structures. I was trying to study the context in which informed consent operates. For a contextual understanding, the various stakeholders involved in the paradigm of clinical trials in India needed to be identified and approached for research. The stakeholders approached for interviews are outlined in the following table:

**Stakeholders involved in the clinical trial paradigm in India
&
Stakeholders approached for interviews (Table 1.)**

Stakeholder	Role/Function
Ministry of Health and Family Welfare (MoHFW)	The Ministry in charge of health policy in India.
Central Drugs Standard	Principal regulatory body which oversees

Ethics in clinical research in India: A survey of clinical research professionals' perceptions, PERSPECTIVES IN CLINICAL RESEARCH, Vol. 4, Issue No. 1, (2013), pp. 4-8; R. Kandhari, *Justice in jeopardy: a qualitative study of institutional ethics committees in New Delhi*, INDIAN JOURNAL OF MEDICAL ETHICS, Vol. 10, Issue No. 3, (2013).

Control Organisation (CDSCO)	the licensing, marketing and trials of drugs in India.
Drugs Controller General of India (DCGI)	Final authority in matters related to approval of new drugs under certain specified categories. His office's approval is necessary to commence a clinical trial.
Indian Council of Medical Research (ICMR)	The apex body for the formulation, coordination and promotion of biomedical research in India.
Central Drugs Research Institute (CDRI)	It is a multidisciplinary research laboratory operating under the aegis of the Council of Scientific and Industrial Research (CSIR). Conducts clinical trials as well.
Institutional Ethics Committees (IECs)	Reviews the research protocol/proposal of the clinical trial studies keeping the welfare of trial participants as top priority.
Trial Investigators	In charge of conducting the trials and are accountable for conduct of the study. They bear the responsibility of ensuring that the informed consent process adheres to the guidelines.
Contract Research Organisations (CROs)	Business that specialises in providing support services to the pharmaceutical, biotechnology, and medical device industries.
Representatives from Pharmaceutical Industry	These representatives were involved in compliance oversight functions and were project leads for clinical trials sponsored by their corporations in India.
Bioethicists	Experts in the field on biomedical research ethics.
Lawyers	Those who have handled cases of medical

	negligence, experts in medical and health law issues in India.
Civil Society	NGO's and other organisations demanding safety of trial participants; watchdogs of clinical research in India.
Trial Participants	Participants involved in clinical trials. Bearers of the right to informed consent.

After identifying the main stakeholders or actors involved in the process of informed consent in clinical research, I went about a systematic procedure to collect the interview data. The step-by-step process will be detailed in the sections that follow.

5.1.2. Site-Selection and Recruitment of Interview Participants

India can be an overwhelming country in which to conduct research owing to the sheer magnitude and diversity of the population. However, since it is my native land, it made access to information slightly easier because of my familiarity with the surroundings. Furthermore, I belong to the same society that I set out to research and a deeper understanding of the Indian society was vital to do the kind of research this thesis warrants.

I required no research permit to conduct research in India. Nonetheless, necessary permissions were sought (and granted) from the Edinburgh Law School Research Ethics Committee and the respective governmental authorities before some officials were interviewed in their official capacity. New Delhi, the capital of the country, was chosen as the base for the six-month period of data collection given that the bodies that regulate clinical research in the country are located there. Mumbai (in the State of Maharashtra) was chosen for accessibility to academics and bioethicists that have been working on clinical research related issues. The state of Madhya Pradesh was the site of the clinical trials that highlighted the debate about ethics of clinical research in India. I mentioned these trials in the introductory chapter. The cities of Indore and Bhopal (in Madhya Pradesh) were chosen to meet with civil society members who highlighted the unethically conducted trials in the region. The investigators approached for this study were spread across public and private

hospitals in New Delhi and Mumbai. For maintaining anonymity, the site location of the Contract Research Organisations (CROs) and the trial participants is not being disclosed.

Research participants were selected through a combination of purposive, snowball, and random sampling method. Purposive sampling was employed to ascertain the first few participants of research. This was based on the multi-stakeholder approach to data collection, therefore, I started from the top of **Table 1**. This kind of sampling was chosen because it is a non-probability sampling where the researcher selects the participants based on her judgment and purpose of research.¹⁴ From the primary research participants identified through purposive sampling, snowball-sampling was done to select the rest of the research participants. Snowballing, or snowball sampling, is a method whereby research participants are chosen from the acquaintances of the existing research subjects. Simply defined, snowballing is “technique for finding research subjects. One subject gives the researcher the name of another subject, who in turn provides the name of a third, and so on.”¹⁵ The simple random sampling was used for the list of sample units or participants (sample basis), where individuals were randomly selected from a database. Access to some participants, especially in the regulatory circle, was granted through gatekeepers or key insiders, who were people with formal or informal authority to control a site and flow of information.

5.2. Process of Data Collection

The dynamics were ever-changing in the field. I had planned for monthly visits to trial site locations across the country to interview trial participants, but I spent most of my time New Delhi. I made intermittent visits to Madhya Pradesh, Maharashtra, and to undisclosed locations of CROs. I ended up travelling as and when a potential interviewee was available for discussion. However, the data collection process followed a skeletal three-phase structure, which proceeded as follows:

¹⁴ J. C. WELMAN & S. J. KRUGER, RESEARCH METHODOLOGY FOR THE BUSINESS AND ADMINISTRATIVE SCIENCES, (Johannesburg, South Africa: International Thompson, 1999).

¹⁵ See W. P. VOGT, DICTIONARY OF STATISTICS AND METHODOLOGY: A NONTECHNICAL GUIDE FOR THE SOCIAL SCIENCES, (London: Sage, 1999).

5.2.1. Phase I of Data Collection

Location: New Delhi

This phase involved conducting interviews with officials from the administrative bodies involved in clinical trial regulation and biomedical research promotion in India. The targeted officials included members of the Indian Council of Medical Research (ICMR), Ministry of Health and Family Welfare (MoHFW), Central Drugs Standard Control Organisation (CDSCO) and the sub-divisions within, and members of Institutional Ethics Committees (IECs) from hospitals and research centres. The aim of this phase of data collection was three-fold: i) to better grasp the clinical trial process and the nuances of the informed consent procedure as understood and managed by the regulatory officials, ii) to note deviations from prescribed procedure in law and the theoretical principle, if any, and use it as a standard for comparisons from data collected in the later stages, and iii) to understand the different perspectives from which these bodies approach the principle of informed consent given their different engagement with the process.

5.2.2. Phase II of Data Collection

Location: New Delhi, Mumbai (Maharashtra), Indore and Bhopal (Madhya Pradesh)

This stage of interviewing focused on the organisations and people that were involved in highlighting the unseen side of the clinical trial industry in India. It also focused on getting various stakeholder views on the implementation of the new rule related to mandatory audio-video recording of the informed consent procedure, which was compulsory for all trial participants when this fieldwork was undertaken, however, it was later limited to vulnerable trial participants. Some bioethicists and doctors, who have been involved in debates around clinical trials in India, contributed their views on some aspects of clinical research and informed consent in the country. The aim of this phase of data collection was to reach out to people who have spoken or written about issues related to informed consent in clinical trials in the country.

5.2.3. Phase III of Data Collection

Location: New Delhi, Mumbai (Maharashtra), and undisclosed locations

In this stage, I tried to get access to trial participants, which turned out to be extremely difficult, especially for the current trials happening in the country. The reasons cited were many, including confidentiality, data protection, and yearlong wait periods to get the requisite permissions.

I visited public and private hospitals and research centres in Mumbai and Delhi to interview investigators running trials in the country. This phase also involved talking to CRO employees (at undisclosed locations), pharmaceutical representatives, lawyers, and activists. However, while I waited at the public hospitals, the dismal reality of poverty and the context within which medical decisions are made was quite evident. But in sharp contrast to it, the research arms of the same public hospitals were quite well-maintained. The professional research centres were even better maintained. The aim of data collection in this phase was to get a complete picture of the various debates plaguing the clinical research spectrum in the country and to see how informed consent fits in the bigger picture.

During the data collection process, I interviewed close to 50 stakeholders. However, I have signed consent forms and email confirmation for use of data from 35 of them. I have attached a copy of the consent form for this research in Appendix IV. However, I decided to exclude data obtained from only verbal consenters who could not be reached again for verification and reconfirmation, this was despite the fact that their consent was fully informed and their data was relevant to the thesis. The following table contains a breakdown of the numbers corresponding to their roles and affiliations.

Number of stakeholders interviewed:* (Table 2.)

Officials from Regulatory Bodies	6
Trial Participants	2
Investigators	8
Institutional Ethics Committee Members	4

Contract Research Organisations	3
Civil Society Members (NGO's, bioethicists, public health activists)	5
Lawyers	2
Representatives of Pharmaceutical Corporations	3

* this only includes people whose data I use for analysis and who either signed the consent form or gave verbal consent and reconfirmed use of their verbatim quotes via email

Having mentioned the process of data collection, I will now outline the design of my interview questions.

5.3. Design of Interview Questions

The interviews took the form of discussions, which were open-ended and semi-structured, and addressed the following themes:

- How does the perception of law and ethics affect the perception of the principle of informed consent? Simply put, is the principle observed by the authorities because it is ethical to do so or is it seen as a legal obligation by the people who engage with it? This question aimed to challenge a lot of assumptions that I had regarding the normative value of the principle of informed consent. This line of questioning helped understand whether the principle is followed because it addresses key ethical values or simply as a tick-box exercise for the purpose of the *formal* process of informed consent in India.
- What role do law and ethics play in bringing about ethical conduct in clinical trials?
- How do officials in the regulatory authorities (CDSCO, DCGI) and at the apex medical research organisation (ICMR) view informed consent in their respective roles?
- How have the various stakeholders in clinical trials in India encountered the principle of informed consent? What challenges did they face during the process of realising (or giving) consent?

- How much has the case *Swasthya Adhikar Manch v. Union of India* (SAM case), the *sub-judice* case that started the legal debate about ethics in clinical trials in India, changed perceptions about the principle of informed consent on the ground, keeping in mind that it led to audio-video recording of informed consent procedure being made mandatory for vulnerable trial participants.
- Is ‘informed consent’ the only way to protect ‘personal autonomy’ of research participants? What factors affect the choice of research participants to volunteer for clinical trials? What would the research participants regard as adequate information to make a decision about volunteering for a clinical trial?
- Are the officials aware of, or responsive to, the vulnerability of the Indian trial participants?

Up until now, the reader was led through a sanitised version of my data collection process. But like any other qualitative researcher, I too encountered some problems while conducting the actual fieldwork. The next few sections will document my research experience on the field and how the field reality was different to the one envisaged during the preparation for fieldwork. Here, I will also be transparent about how I got access to different stakeholders so that future researchers can identify the dos and don'ts for conducting similar research.

5.4. Ground Reality: Access to Research Participants

There were some limits to adopting a multi-stakeholder approach to data collection, as there was limited accessibility to certain stakeholder groups, like trial participants and government officials. Trial participants are bound by confidentiality agreements with the trial sponsors. Therefore, it is almost impossible to conduct an interview with them regarding their participation in the trial and the procedures involved. Moreover, access to trial participants is difficult, as no investigator would compromise a trial study by giving access to their trial participants. From another perspective, government officials in India are in an elite position, and it is often impossible, as an independent researcher, to establish a connection with these

officials. In a survey conducted by a Hong-Kong based think-tank, Political and Economic Risk Consultancy (PERC), India was ranked as Asia's most over-regulated country, with a highly inefficient bureaucracy, with a score of 9.21 out of 10.¹⁶ The same survey revealed that the Indian bureaucracy is a power centre in its own right and access to bureaucrats for common people is almost impossible. To put this into perspective, I was just another commoner who had difficulty getting access to the bureaucrats.

I started out by approaching members of various regulatory bodies through email. After a long wait period, three participants responded to the emails. A copy of the email sent to research participants is attached in Appendix V. I tried to contact officials on the telephone numbers provided on the official government websites, but without much success. Lastly, I personally approached the officials within these regulatory bodies and other government organisations at the institutional premises. At first, I requested the officials to consider being "interviewed", but barring one almost all of them turned down the request. Instinctively, I tried to persuade them to "talk and discuss" issues pertaining to clinical research in the country. This approach was much more successful. Most of the officials allowed the information to be used for research purposes on the condition of confidentiality, which has been respected throughout the thesis.

As mentioned above, trial participants are bound by confidentiality agreements with the trial conductors. I interviewed eleven trial participants, but only two signed the consent form and I could not relocate the rest to reconfirm their verbal consent. Hence, I use data from only two trial participants. One of them was an ex-trial participant and was not enrolled in any trial study. The other participant had not been administered the trial drug, but had been led through the consent procedure for the trial study. It was the investigator of the study who invited me to talk to the trial participant.

The investigators of trial studies were selected at random through the Clinical

¹⁶ As cited in P. L. Joshi & R. Kumar, *A survey of positive and negative aspects of the Indian administrative bureaucratic system*, INTERNATIONAL JOURNAL OF INDIAN CULTURE AND BUSINESS MANAGEMENT, Vol. 4, Issue 6 (2011), pp. 658-684.

Trial Registry of India (CTRI) web platform which is an online database of clinical trials being conducted in India.¹⁷ The email addresses and contact details of investigators and sponsor representatives are mentioned on the data sheets available online. I selected my sample size at random and met investigators who responded to my emails or telephone calls. Some investigators introduced me to the Institutional Ethics Committee (IEC) members and some had themselves served as members of ethics committees at their respective institutes. This is how I also got access to IEC members.

The Contract Research Organisations (CROs) were selected at random from an exhaustive list of CROs operating in India. I was invited to visit the premises of one of the CROs. I personally met and spoke to the clinical research associates of the other two CROs.

I shortlisted five global pharmaceutical corporations conducting trials in India and sent emails to key contact persons in the clinical trial operations teams. Three people responded to the emails and I met two of them at their chosen time and place. One of the representatives spoke to me online through the WEBex communications platform, the conversation was recorded for the communication files of the corporation.

The members of the civil society were screened from the newspaper articles, periodicals, journals, and through snowballing methods. Communication was set up through gatekeepers and through email requests. The lawyers selected for the research were approached through my own professional legal network.

5.4.1. Problems with consent forms and audio recording

When I approached the government officials for interviews, none were willing to sign a written consent form or agreed to audio recording of the interviews. They all gave verbal consent to allow the use of the data from discussions. They only agreed to speak to me on the condition of “full confidentiality”. I followed the guide for elite

¹⁷ Clinical Trials Registry of India website, available at <http://ctri.nic.in/Clinicaltrials/login.php> (last accessed on June 2, 2018)

interviewing for these officials.¹⁸ When I asked the participants if they were comfortable with being audio-recorded, they appeared extremely uncomfortable at the prospect. During the entire fieldwork period, I took written notes, sometimes in alphabetic shorthand to minimise loss of data. After each session, I typed up all the data, in a neater language, into a word document to minimise any chances of mistakes that might arise from having to remember the conversation later and emailed this back to these participants.

Some stakeholders like the representatives of pharmaceutical corporations, trial participants, CRO employees, and a few investigators did not sign a written consent form and requested confidentiality, but permitted me to use the information for the research. I communicated these issues from the field to my PhD supervisors and to the Ethics Committee members at Edinburgh. It was agreed that the information would only be used if discussion/interview notes were sent back to these participants for comments. All the discussion notes were typed with verbatim quotes and paraphrases and were sent back to the research participants for their comments. Most participants responded by permitting the use of their quotes as long as confidentiality was maintained. As best as I could, I have anonymised all the research participants in the thesis.

From my own perspective, as someone researching the principle of informed consent, it was insightful to perceive how participants responded to the consent forms handed to them for this research. I gave complete information about myself and my research project to the participants, explained to each participant their rights as mentioned in the consent form, read out the contents of the consent form, but most stakeholders refused to sign the paper. Some joked about my background as a lawyer, saying they would not sign a paper given to them by a lawyer. It was important for the research participants to create a trust-based relationship with me, but without the need for formal papers.

¹⁸ D. Richards, *Elite Interviewing: Approached and Pitfalls*, POLITICS, Vol. 16, Issue no. 3, (September 1996), pp. 199-204.

5.4.2. Acknowledging limits of this qualitative research

I realise that I have barely scratched the surface of the problem in terms of my qualitative inquiry. A major limitation of this empirical research is that people who responded to the emails that I sent out were the ones who either believed in the ethics of clinical research, or, at least, had proper knowledge of them. These people did not mind expressing opinions, were educated, spoke fluent English and mostly came from a privileged stratum of the society. A significant proportion of stakeholders interviewed for this research were government officials, trial investigators, CROs, and employees of pharmaceutical corporations. The number of trial participants was too small to make general claims. Hence, for the purpose of data analysis I have used previously conducted empirical research by other scholars to bolster my research findings. Moreover, some claims of the research participants for this research could be true in their individual experiences with the system, but my sample size is too limited to make generalisations regarding any such claims.

Another limitation of the thesis is that the empirical claim of the thesis, which will be outlined in Chapter 8, might lead some readers to think that this thesis is about bureaucratisation or about the nature of bureaucracy. Although I use terms like “procedural necessity” and “tick-box exercise” they are used for the process of informed consent effectuated by researchers/investigators and not the regulatory officials. It needs to be made clear that the interviews with the stakeholders, including regulators, included their perceptions on the nature of informed consent, i.e., what they think about informed consent or its various features. The research findings are not about how *all* stakeholders view consent in their given roles. The only stakeholders who spoke to me about consent from their respective roles within the (biomedical research) paradigm were the researchers as they are the ones upon whom the duty to take consent rests. The other stakeholders only come into the picture when there is problem with the process as performed by the researchers. The regulators I interviewed did not say anything that could be bracketed as their official position on the process of consent, except when asked about the need for stricter laws to make researchers more ethically complaint. Their views on informed consent echo the views of the researchers. That is hardly surprising because the officials I

interviewed had themselves been researchers at some point of their careers.

Another factor to take into consideration is that I spoke to 6 officials from the regulatory and research coordinating bodies, 4 of whom had been researchers themselves and were affiliated to ICMR, which is often (mistakenly) considered a regulatory body, but is not a regulatory body by its mandate. I spoke to 8 investigators and 4 Ethics Committee members. The Ethics Committee members had previously been investigators of studies. This means that 16 (of 35) of those that I spoke with have primary experience of informed consent in research from their experiences as researchers/investigators, and in another capacity only secondarily. This makes it predominantly an investigator-perspective thesis. Therefore, the scope of the empirical claim is limited to researchers/investigators.

5.5. Data Analysis

The development and identification of variables did not take place prior to data collection but instead was carried out as part of the data collection process. Consequently, the variables or concepts were mostly initiated by the interviewees/participants and further developed and conceptualised by me. This is an important aspect of the iterative process. Data was collected until theoretical saturation was reached,¹⁹ which means that collection of data continued until no new or relevant data emerged regarding informed consent.

According to Strauss and Corbin, in grounded theory methodology, interview questions should give as little guidance as possible to allow the interviewees to talk about what is of importance to them regarding a given context.²⁰ Therefore, the data collected can be patchy and unstructured. After the collection process is over, the data is analysed through identification of themes and development of a coherent conceptual framework around those themes. As I employed tools from this methodology for data coding, I was required to extract phenomena or experiences significant to the interviewee by assigning a conceptual label, known as a 'code'. Several codes were then grouped into more abstract 'categories' which eventually

¹⁹ STRAUSS & CORBIN (1998), *supra* note 6.

²⁰ *Id.*

formed the basis for developing themes. As will be evident in the next section, few of the categories and themes that emerged during analysis were irrelevant to the principal research question, but for the purpose of demonstrating the steps of my data analysis, I have shown all the themes and categories.

5.6. Coding and Development of Themes

I tried to use the software QDA Miner Lite v1.4.6, an open source software, to develop codes and categories from the interview transcripts. However, it was much easier to manually code and categorise the data, as the number of interview transcripts was quite small. I worked through each transcript using line-by-line coding to note down the themes and categories along the margins of the sheets. Keywords and main phrases were noted on differently coloured post-it notes and stuck on a board. This was useful in categorising the data under different post-it notes. These post-it notes, carrying categories, were later arranged in a logical order on a separate sheet of paper. During the progression of coding, interview data belonging to a particular code and category was placed under the corresponding post-it note. The QDA software was used to retrieve all the text related to the phrase ‘informed consent’ to double-check if I had lost any data during the process of manual coding. All interview data categorised under informed consent was extrapolated into different themes. These themes were initially categorised as follows:

<ul style="list-style-type: none"> • Process of consent* • Law as a solution* • Role and limits of ethics and law*
<ul style="list-style-type: none"> • Drop outs, retention rates – measure of success of informed consent? *
<ul style="list-style-type: none"> • Bioethical Health Regulatory Authority of India Bill, BHRAI Bill [x] • Developments in other countries [x]
<ul style="list-style-type: none"> • No objectivity in journalism, sensationalism of trials*
<ul style="list-style-type: none"> • Acknowledgment of the role of the civil society in the government sector [x]
<ul style="list-style-type: none"> • Manipulation of clinical trial data [x]
<ul style="list-style-type: none"> • How do we make people more ethical? Kantian ethics-treat people as ends

and not just means to an end *
• Do strict laws help? *
• Practical India-specific solutions *
• Taking and giving consent were circumstantial acts *
• Informed consent cannot be directive *
• How to ascertain that information related to trials is understood by the participants? *
• Is knowledge of the law under which you're doing something wrong necessary? [x]
• We cannot apply western standards of quality control etc, [x]
• Universalist western ethics? [x]
• Risks v. Benefits of clinical trials in India [x]
• Should trials only be for public health needs? [x]
• No capacity or possibility of on-site inspections *
• Oversight mechanisms *
• Conflict of interests in IECs and compositional problems [x]
• New regulations, problems, are they being diluted? [x]
• Clinical trial industry: a structurally violent industry? [x]
• How do we read deaths from clinical trial data, causation? [x]
• Undue Inducement: not an unfair deal in countries like India *

[x] themes not included in final thesis/ * themes condensed into broader themes

Many of these themes fell out of the scope of the thesis. They corresponded to the broader gamut of clinical trial regulation and included participant views on other ethical issues in clinical research in India. However, the research findings and themes that explained the phenomena and process of the principle of informed consent that were central to this thesis were:

-
- 1. The three conditions of consent in trials through the lens of different stakeholders: Voluntariness, adequacy of information, capacity/competence to consent**
-
- 2. Participant views on economically and socially disadvantaged participants**
-

3. Different perceptions on agency of trial participants
4. Law or Ethics? The ambivalence around legal solutions
5. Who does the Informed Consent Form Protect?
6. Lack of oversight mechanisms
7. Current regulatory norms and problems therewith
8. How to measure the success of informed consent procedure?
9. Difference in informed consent to treatment and consent in trials
10. Informed Consent cannot be separated from the overall context of clinical trials in the country- Controversy in perspective.

For the purpose of final data analysis, a *contrasting method* was employed where these research findings were pitted against the ethical, legal, and empirical literature on the topic and were ultimately condensed into five major themes. These themes will be elaborated upon in the next two chapters. The first three themes correspond to the three broad ethical and legal requirements of informed consent, viz., voluntariness, adequate information, and competence/capacity. The other two correlative themes concern autonomy as the rationale of informed consent and the role of law and ethics in the realisation of informed consent. I have used the qualitative interpretative approach to the semi-structured interviews, which means that analysis is presented alongside theoretical discussions.

5.7. Triangulation

Data triangulation implies the collection of data from different participants in a given setting, or from different stages in the activities of the setting and/or, if appropriate, from different sites of the setting. Triangulation is done through a mix of methods or data types to shed light upon various viewpoints or to validate the claims that might arise in the initial stages of the study.²¹ The multi-stakeholder approach, as explained above, proved to be quite effective for data triangulation because it allowed me to verify information given by one stakeholder with that of another stakeholder. During

²¹ P. BANISTER, ET AL., *QUALITY METHODS IN PSYCHOLOGY*, (Buckingham: Open University Press, 1994), p. 146; *See also* E. G. GUBA & Y. LINCOLN, *FOURTH GENERATION EVALUATION*, (Newbury Park: Sage Publishers, 1989),

the interviews, as a triangulating technique, it was useful to pit one stakeholder view against the other to verify opposing statements by different stakeholders on some issues. In the later stage, the findings from the interviews were contrasted and bolstered through comparison with existing empirical research studies. This method of triangulation called “methodological triangulation”²² was constantly used in the analysis and will be evident in the following chapters.

5.8. Data Storage

During the fieldwork planning stage it was decided that interviews would be audio-recorded, however, things quickly changed in the field. People showed disinterest in interviews if the suggestion to be audio-recorded was put forward. Most participants only agreed to talk if they were not being audio-recorded. Therefore, quite early into the fieldwork I took the decision in consultation with my supervisors that none of the discussions/talks/interviews will be audio-recorded. I, therefore, took handwritten notes, sometimes using alphabetic shorthand, during interactions with the participants.

The data is stored on my personal laptop and is kept in one external hard-drive for back-up purposes. All the data is password protected for security. The files will only be shared with supervisors via *dropbox* or email, if necessary. The data will remain stored on my personal computer for the time required to complete the thesis and disseminate the findings. The data will be stored for University purposes for 10 years as prescribed by the Research Ethics and Integrity Committee, School of Law at the University of Edinburgh, and in accordance with the UK Data Protection Act, 1998.

5.9. Conclusion

It is important that the methodology utilised to answer the research questions stands up to scrutiny. Therefore, this chapter has explained how I utilised some tools from the grounded theory methodology to collect and code the interview data that I accumulated from different stakeholders. During the fieldwork, I had to adapt to

²² See generally U. FLICK, *METHODOLOGICAL TRIANGULATION IN QUALITATIVE RESEARCH*, (Sage Publishers, 2007)

issues like participants' refusal to sign consent forms, constant change in interview locations, frequent cancellations of previously agreed to interviews, and inaccessible bureaucrats. Despite all those issues, I did manage to collect data from *all* the stakeholders that I had identified as *instrumental* in the process of informed consent in India. A grounded thesis, which works from the bottom-up in terms of the principle and process being described through the words of the practitioners themselves, has been developed using a *mixed* methodology. This grounded thesis (which will be elaborated upon in the final chapter) has been developed to identify the reason for the discrepancy between the ethical principle, the legal doctrine, and the practice of informed consent. The next chapter will present the research findings and analyse them in comparison with the existing academic literature in the area. What this method of analysis highlights is the fact that the practitioners do not often view the principle and the process of informed consent as is envisaged in theory.

RESEARCH FINDINGS AND ANALYSIS: THE ESSENTIALS

6.0. Introduction

This chapter aims to answer the question: How is the principle of informed consent perceived by the different stakeholders involved in the process of acquiring it in clinical research in India? This chapter will use examples of informed consent “in action” against the backdrop of informed consent in ethical and legal theory. Informed consent “in action” will consist of my research findings accumulated over the period of six months interviewing various stakeholders in clinical research in India.

Earlier chapters in this thesis firmly established that informed consent is considered the ethical and legal cornerstone of medical research involving human subjects.¹ In bioethics, for consent to be ‘informed’ in the context of a clinical trial, an individual must: a) have the capacity to consent, b) be fully informed about the trial, and c) have given the consent voluntarily.² Under the Indian law governing clinical trials,³ informed consent must be:

- vi) Freely given and must be obtained in writing on an informed consent form.
- vii) The Investigator must have provided information in a nontechnical and understandable manner.⁴

¹ See J. W. BERG, ET AL., INFORMED CONSENT: LEGAL THEORY AND CLINICAL PRACTICE, (New York: Oxford University Press, 2001, 2nd edn); J. KATZ, THE SILENT WORLD OF DOCTOR AND PATIENT, (New York: Free Press, 1984); R. FADEN & T. BEAUCHAMP, A HISTORY AND THEORY OF INFORMED CONSENT, (Oxford University Press, 1986); T. L. BEAUCHAMP & J. F. CHILDRESS, PRINCIPLES OF BIOMEDICAL ETHICS, (New York: Oxford University Press, 2009, 6th edn), pp. 77-93; National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research, *The Belmont Report*, (Washington: US Government Printing Office, 1979); R. J. LEVINE, ETHICS AND REGULATION OF CLINICAL RESEARCH, (2nd edn., New Haven: Yale University Press, 1988), pp. 95-153.

² Although Faden and Beauchamp write about five main elements of consent; viz, i) Disclosure ii) Comprehension of information iii) Voluntariness iv) Competence of the individual giving consent v) Consent (decision of consent). Comprehension and consent are taken to be imbedded in the other three conditions mentioned above. See R. FADEN & T. BEAUCHAMP, A HISTORY AND THEORY OF INFORMED CONSENT, (Oxford University Press, 1986), p. 274.

³ Schedule Y, Drugs and Cosmetic Rules, 1945 (hereinafter ‘The Rules’), as appended to Drugs and Cosmetics Act, 1940.

⁴ The Rules say that the Investigator must have informed the study subject verbally and through the patient information sheet (PIS).

- viii) The patient information sheet as well as the informed consent form should have been approved by the ethics committee and furnished to the Licensing Authority (DGCI).
- ix) In cases of incapacitated persons⁵ consent may be obtained from a legally acceptable representative.⁶
- x) If the trial participant or his/her legally acceptable representative is unable to read/write - an impartial witness should be present during the entire informed consent process who must append his/her signatures to the consent form.

At a cursory glance, the ethical and legal requirements of informed consent in clinical trials in India do not seem to be at odds with each other. They can broadly be classified under *voluntariness*, *full disclosure of information*, and *competence* to consent. Chapter 4 showed that when the principle of informed consent is put into practice, it appears that the law has made an uneasy compromise with the ethical theory of informed consent.⁷ Scholars like Schuck and O'Neill have identified the considerable gaps that exist between informed consent in theory and practice.⁸ Schuck recognizes three different versions of informed consent, viz., informed consent “in books”, “in the mind”, and “in action”. According to Schuck informed consent “in books” has been developed primarily by courts, a physician’s version of informed consent is the version that exists “in the mind” of the physician, and informed consent “in action” is what is practiced in a real setting by the clinicians. He notes that considerable differences and varying opinions exist between the three, especially in the academic opinion regarding the scope and applicability of informed

⁵ The Rules give example of an unconscious person or a minor or those suffering from severe mental illness or disability.

⁶ The Rules says that a legally acceptable representative is a person who is able to give consent for or authorize an intervention in the patient as provided by the law(s) of India, viz., guardian for a minor and legal curator for the mentally ill and disabled.

⁷See generally A. J. Weisbard, *Informed Consent: The Law's Uneasy Compromise with Ethical Theory*, NEBRASKA LAW REVIEW, Vol. 65, (1986). In this article the author has convincingly argued, by analysing case law from the USA, that if law is to be judged by how successful it was in implementing the moral vision of informed consent as articulated by the philosophers, then it has greatly failed.

⁸ P. H. Schuck, *Rethinking Informed Consent*, YALE LAW JOURNAL, Vol. 103, (1994), at p. 903; See N. C. MANSON & O. O'NEILL, *RETHINKING INFORMED CONSENT IN BIOETHICS*, (Cambridge University Press, 2007), p. 212, p. 11.

consent. Borrowing from Schuck's classification, I propose that, in the case of clinical trials, three versions of informed consent can be found, viz., informed consent "in ethics", "in legal doctrine", and "in action".

This chapter is divided into three sections corresponding to the three broad ethical and legal requirements or essentials of informed consent. I first give an account of each feature in theory and follow it up by talking about each essential feature *in action*. This format of data presentation has been chosen to show the how informed consent appears in academic literature versus how stakeholders view it in real clinical research practice.

6.1. VOLUNTARINESS

Populations of developing countries are said to be subject to a variety of undue/coercive influences that erode their voluntariness.⁹ Empirical studies across Asia and Africa have been undertaken by numerous scholars to assess the voluntariness of clinical trial participants or research subjects, but scholars have had difficulties interpreting these studies due to the wide variety of assessment approaches used.¹⁰ Up until now, there are no well-accepted *adequate* measures of voluntariness in research settings,¹¹ although attempts have been made to develop more comprehensive approaches to assess voluntariness of consent to research.¹² One

⁹ P. A. Marshall, *Informed Consent in International Health Research*, JOURNAL OF EMPIRICAL RESEARCH ON HUMAN RESEARCH ETHICS, Vol. 1, (2006), pp. 25-41; C. A. Pace & E.J Emanuel, *The ethics of research in developing countries: assessing voluntariness*, THE LANCET, Vol. 365, Issue No. 9453, (January, 2005), pp. 11-12; N. Mamotte & D. Wassenaar, *Measuring Voluntariness of Consent to Research: An Instrument Review*, JOURNAL OF EMPIRICAL RESEARCH ON HUMAN RESEARCH ETHICS, Vol. 10, Issue No. 2, 2015, pp. 121-131.

¹⁰ P. S. Applebaum, et al., *Voluntariness of Consent to Research: A Preliminary Empirical Investigation*, IRB: ETHICS AND HUMAN RESEARCH, Vol. 31, Issue No. 6, (November-December, 2009).

¹¹ Mamotte & Wassenaar (2015), *supra* note 9, in a Wellcome Trust funded study on the voluntariness of consent to research systematically reviewed existing empirical studies of voluntariness of consent to research to establish how voluntariness of consent to research has been assessed in the past and whether a valid and reliable measure exists. They concluded that measures so far were inadequate to assess voluntariness in consent.

¹² For example, in the study conducted by Mamotte & Wassenaar (2015), *Id.*, the authors identified 'offers, pressures, and threats' related to research participation, as inspired from the works of sociologist Talcott Parsons, who conceptualized these mechanisms defining ways in which one person can exert influence on the decisions of another. They used a modified version of MacArthur's Coercion Scale and made a voluntariness ladder based on the variables of offer, pressures and threats.

of the major reasons attributable to the uncertainty in measuring voluntariness is the lack of consensus in the definition of what it entails.

The different definitions of voluntariness include Beauchamp and Childress' definition where a person is said to act voluntarily "if he or she wills the action without being under the control of another's influence".¹³ Nelson et al., conceptualise voluntariness as intention to consent with the absence of exposure to controlling influences or conditions.¹⁴ In Beauchamp's definition the 'controlling influence' entails personal influence whereas in the definition given by Nelson and colleagues it entails personal, economic, and *other* influences. Olsaretti has defined involuntariness as lack of acceptable alternatives to research participation.¹⁵ Wertheimer and Appelbaum have proposed to morally assess the legitimacy of influences to understand when consent is non-voluntary.¹⁶ Some scholars opine that clinical research conducted by developed country researchers in developing countries leads to non-voluntary participation due to the nature of monetary or medical incentives offered that the trial participants might not be in a position to deny.¹⁷ This

Coercions scales have been used in previous empirical works. *See further*, W. Gardner, et al., *Two scales for measuring patients' perceptions of coercion during hospital admission*, BEHAVIOURAL SCIENCES & THE LAW, 1993; Vol. 20, (1993), pp. 307-321; G. Hoyer, et al., *Paternalism and Autonomy: A presentation of a Nordic study on the use of coercion in the mental health system*, INTERNATIONAL JOURNAL OF LAW AND PSYCHIATRY, Vol. 25, (2002), pp. 93-108; K. L. Dugosh, et al., *Measuring coercion to participate in research within a doubly vulnerable population: Initial development of the Coercion Assessment Scale*, JOURNAL OF EMPIRICAL RESEARCH ON HUMAN RESEARCH ETHICS, Vol. 5, (2010), pp. 93-102.

¹³ T. BEAUCHAMP & J. CHILDRESS (2009), p. 132, *supra* note 1.

¹⁴ R. M. Nelson, et al., *The concept of voluntary consent*, AMERICAN JOURNAL OF BIOETHICS, Vol. 11, Issue No.8, (2011), pp. 6-16.

¹⁵ S. Olsaretti, *Freedom, force and choice: Against the rights-based definition of voluntariness*, JOURNAL OF POLITICAL PHILOSOPHY, Vol. 6, (1998), pp. 53-78.

¹⁶ They argue that voluntariness cannot be a completely value-free concept as to morally assess the legitimacy of an influence over a person would require choices that are inherently value-laden. *See* P. S. Appelbaum, *Can a theory of voluntariness be a priori and value-free?*, AMERICAN JOURNAL OF BIOETHICS, Vol. 11, Issue No. 8, (2011), pp. 17-18; A. Wertheimer, *Voluntary consent: Why a value-neutral concept won't work*, JOURNAL OF MEDICINE & PHILOSOPHY, Vol. 37, (2012), pp. 226-254.

¹⁷ P. A. Marshall (2006), *supra* note 9. For monetary incentive considered as undue inducement to participation, *See* N. E. Kass, et al., *Motivations, Understanding, and Voluntariness in International Randomized Trials*, IRB: ETHICS & HUMAN RESEARCH, Vol. 27, (2005), Issue No. 6, pp. 1-8; J. Koen, et al., *Payment of trial participants can be ethically sound: Moving past a flat rate*, SOUTH AFRICAN MEDICAL JOURNAL, Vol. 98, (2008), pp. 926-931. For medical incentives considered as inducement leading to non-voluntariness *see* Kass et al., (2005); C. Pace & E. J. Emanuel, *The Ethics of Research in Developing Countries: Assessing Voluntariness*, THE LANCET, Vol. 365, (2005), pp. 11-12; R. M.

lack of consensus over the concept of voluntariness has led researchers to raise various concerns about voluntariness, as understood by them, to consent in clinical trials.

Appelbaum has suggested that to begin understanding the notion of voluntariness, one must understand how law has defined voluntariness, he writes:

[f]rom the perspective of the practitioner or researcher trying to understand the implications of the requirement that consent must be voluntary to be valid, the key question is not how philosophical thought has characterized voluntary action over the millennia—it is how law and regulation view voluntariness in the context of informed consent.¹⁸

In the same paper, Appelbaum suggests that theorists could adopt either of two approaches to develop a theory of voluntariness. The first approach would be to begin with *a priori* principles of the conditions of voluntary choice, an approach reflected in the definition of voluntariness given by Nelson et al (as mentioned above). Appelbaum contends that in Nelson et al's attempt of developing a *value-free* theory of voluntariness, they did not rely on legal approaches to voluntariness. He explains that law accepts some external pressures as legitimate that might otherwise negate voluntariness (like a spouse saying, "Stop drinking! Or I am leaving you"), while it recognises others as illegitimate (like a doctor saying, "Sign up to this trial, or I will never treat you again"). This distinction between legitimate and illegitimate external pressures is based on choices that are inherently value-laden. The second, and a more realistic, approach would require the theorist to acknowledge that the process of informed consent is governed by a set of legal rules, after which extrapolation of theory could come from the legal concept of voluntariness as applied in similar situations. Wertheimer approves the latter approach – an opinion that I support because it corresponds to the idea that informed consent is carried out in the shadow of the law. Wertheimer has suggested that any approach that aims to recognize the importance of context for explaining the concept of voluntariness would begin not with *a priori* principles, but with some indication of how the law has

Nelson, et al., *The Concept of Voluntary Consent*, AMERICAN JOURNAL OF BIOETHICS, Vol. 11, Issue no. 8, (2011), pp. 6-16.

¹⁸ Appelbaum (2011), *supra* note 16.

understood voluntariness.¹⁹ These philosophers accept that any a priori approach to conceptualizing voluntariness of consent is much less likely to be helpful in the very treatment or research settings in which it is meant to be applied.²⁰ Hence, we must look at the legally accepted version of voluntariness as a starting point for further inquiry.

Applebaum, Lidz, and Klitzman argue that for legal purposes an act “is presumed to be voluntary if no evidence exists that someone else has unduly influenced it or coerced the person deciding.”²¹ This definition holds up to the law in India as well. Schedule Y on informed consent requirements holds that consent must be ‘freely given’. The Indian Contract Act, 1872, says, “consent is said to be free when it is not caused by coercion or undue influence or fraud or misrepresentation or mistake.”²² Simply understood, consent is deemed to be free consent when there is absence of evidence of undue influence, coercion and misrepresentation. For the purposes of contract law, each of the conditions of coercion, undue influence, fraud, misrepresentation, and mistake have been given legal definitions under the Act (Sections 14-21 in particular). However, such definitional clarity is not present for the law of informed consent. The definitional clarity is lacking mostly because it is hard to ascertain the exact legal status of consent forms.²³ They seem to be contractual in nature and give rise to contractual relationships but are not *sensu stricto* contracts.²⁴ As there is no clear legal definition of voluntariness in the law of

¹⁹ A. WERTHEIMER, COERCION, (Princeton, NJ: Princeton University Press, 1987).

²⁰ Appelbaum (2011) and Wertheimer (2012), *supra* note 16.

²¹ P. Appelbaum, et al., *Voluntariness of Consent to Research*, HASTINGS CENTER REPORT, (2009), pp. 30-39, at p. 32.

²² Section 14, Indian Contract Act, 1872.

²³ See G. Laurie & E. Postan, *Rhetoric or Reality: What is the Legal Status of Consent Form in Health-Related Research?*, MEDICAL LAW REVIEW, Vol. 21, Issue No. 3, (2013), pp. 371-414. This paper shows that the legal status of consent forms is not clear in the UK. Although it is in an evolutionary stage especially in terms more legal protection being afforded to tissues under property rights. Nevertheless, the paper argues that it would be undesirable to resort to legal remedies in governance of research relationships as they depend crucially on trust and are always evolving. The authors argue that law tends to treat consent as a one-off event, which a counterproductive and inappropriate approach because given the nature of clinical research relationships, informed consent cannot be caught in a written document.

²⁴ The Maryland court in the Grimes case has recognised that consent forms are agreements that create contractual relationships between investigators and subjects, which imply legal duties, and they are brought before court as evidence of the existence of such a relationship, *see* Grimes v. Kennedy Krieger Institute, Inc., 366 Md. 29, 782 A.2d 807 (Md. 2001). However, they are not *sensu stricto* a

informed consent in clinical trials, the next step is to look for voluntariness in the ethical guidelines as they are more situational and elaborate.

The Ethical Guidelines for Medical and Health Research on Human Participants (hereinafter the guidelines) released by the ICMR do not define voluntariness per se. They do, however, talk about monetary and medical incentives that should not be large enough “as to make prospective participants consent readily to enrol in research against their better judgment, which would then be treated as undue inducement.”²⁵ The guidelines leave it for the Ethics Committees (ECs) to decide what kind and amount of compensation would be tantamount to ‘undue inducement’.²⁶ It is here that we notice the stark distinction between the law and ethical guidelines. Law is cautious about getting inside the workings of human decision-making to disentangle the web of causal influences, and even more cautious about deciding when one of those influences become determinative enough to void a person's choice. However, the drafters of guidelines chose one *controlling influence*, large monetary incentive, to be determinative enough to void a person's choice.

contract because the research subject can opt-out at any stage without penalty; this makes the research subject immune to contractual obligations on her part. However, Humphreys argues that despite such an overriding right to withdraw, the consent form seems to have all elements of a contract. Nevertheless, his claim lacks universality because not all consent cases in clinical research involve consideration, which limits his argument to only those that do. Moreover, the right to withdraw at any time makes it a quasi-contract at best. *cf* S. Humphreys, *Entering a clinical trial: consent and contract – a consideration*, THE INTERNET JOURNAL OF LAW, HEALTHCARE AND ETHICS, Vol. 6, Issue No. 2, (2008). It is pertinent to note that theorists eventually do borrow language from contract law when talking about coercion, undue influence, misrepresentation, and mistake, as situations that lead to vitiation of consent. In fact, I do so in the thesis as well. But the exact status of informed consent under contract law remains somewhat of an uncertainty. Moreover, the failure of tort law to deal with lack of informed consent cases has led some scholars to suggest contract law as an alternative to problems of informed consent, *see* M. L. Norton, *Contract Law as a Viable Alternative to Problems of Informed Consent*, THE CATHOLIC LAWYER, Vol. 21, Issue No. 2, (2017).

²⁵ Indian Council of Medical Research (ICMR), Ethical Guidelines for Biomedical Research on Human Participants, (2006), p. 25, available at http://www.icmr.nic.in/ethical_guidelines.pdf (last accessed on June 2, 2018). In fact, the updated Ethical Guidelines released by the ICMR in 2017 are very similar in content, especially pertaining to the essentials, to the 2006 guidelines. *See* ICMR, National Ethical Guidelines For Biomedical and Health Research Involving Human Participants, (2017), available at http://www.icmr.nic.in/guidelines/ICMR_Ethical_Guidelines_2017.pdf (last accessed on June 2, 2018)

²⁶ *Id.*, p. 38.

Having taken note of how voluntariness is understood in ethical guidelines and in law; let us now see how some stakeholders involved with informed consent *in action* in India understand voluntariness.

6.1.1. VOLUNTARINESS IN ACTION

Two trial participants agreed to be interviewed by me. Their experience illustrates how they encountered the principle of informed consent in practice.²⁷

1st trial participant (hereinafter ‘A’) - BA/BE studies: The ex-trial participant had been part of many BA/BE (bioavailability/ bioequivalence) studies²⁸ and used the income from trials to supplement his major source of family income, which was not sufficient for him, his wife, and his three children. He told me that he sometimes encouraged his wife to become a participant too. According to A, the recruiters had told him that the risk for participating in BA/BE studies was quite low, so he preferred going for multiple screenings. He told me that these screenings were usually held at various CRO²⁹ facilities for determining whether the volunteers fit the inclusion criteria for the trial study. The CROs also paid people who turned up for the screenings irrespective of whether they passed the screening or not. When one passed the screenings one would be taken through the consent procedure and the participant would get the amount fixed by the CRO for becoming a trial participant. The ex-trial participant said that he was one of the several people who the *bichauliya* (intermediary) contacted to show up for screenings. When asked whether if the

²⁷ For reasons mentioned in the previous chapter, it was almost impossible to find current trial participants willing to participate in the research and also who were willing to sign a consent form for it. The two participants here do not represent the experiences of majority of trial participants in India, their experiences are being shared because they highlight other important aspects of the nature of consent in India.

²⁸ BA/BE are Bioavailability and Bio-equivalence studies. Data generated through BA/BE studies is required for the development of both new drug products and their generic equivalents. Bioavailability is a measurement of the rate and extent to which a therapeutically active chemical is absorbed from a drug product into the systemic circulation and becomes available at the site of action. Bio-equivalence means there are no clinically significant differences between the bioavailability of two drugs. See D. J. Birkett, *Generics – equal or not?*, AUSTRALIAN PRESCRIBER, (August 1, 2003).

²⁹ A Contract Research Organisation (CRO) is a business that specialises in providing support services to the pharmaceutical, biotechnology, and medical device industries. Support services include performing laboratory services, data management, preclinical services and clinical trial management, etc. These services are outsourced to CROs on a contractual basis.

studies turned out to be riskier than presumed he would still choose to participate in the trial, the participant said that he would make the same choice again. Regarding compensation for participation, the participant said that sometimes he could negotiate on the compensation rates but most of the times the rates were fixed.

The experience of *A* shows that he had agreed to consent even before he passed the screening. He perceived the BA/BE studies as low risk and viewed participation as an opportunity to supplement his family's income. Yet had the risk been higher he would nonetheless still have volunteered. What they might or might not have told him at the consent sessions made little difference to him. He even spoke about the possibility of negotiating compensation rates. While *A* was clearly motivated by payment that would help to support him and his family, trial participant *B* below had a somewhat different perspective.

2nd trial participant (hereinafter 'B'): This participant had only recently consented to becoming part of a trial for testing a bio-similar compound;³⁰ hence, the trial drug had not been administered to him yet. On why he chose to be part of the trial, the participant said:

I was told it will be randomised so they will not know which one will receive which injection...we will all get free drugs and I think that was my main reason to take part in this study. The regular dose I get is lakhs [a hundred thousand] of rupees a month, I cannot afford it. This at least gives me at least the normal one I use regularly or the new drug, which they tell me, are both completely similar, and it is free. I would have been stupid to miss this.

On being asked whether he received full and complete information from the doctors who were also the investigators for the study, the trial participant said that he trusted them and that they had told him "all that I need to know". He mentioned that he had faith in the people involved in the trial as it was going to be conducted at one of the best hospitals in the country.

The experience of *B* shows that his motivation to join the trial stemmed from the monetary and health benefit he was going to derive from the study. He was going

³⁰ When a biologic's formula is no longer protected by a patent, other companies can release a drug with the same chemical composition, thereby driving the cost down. That new biologic drug is a bio-similar. Bio-similar compounds are not identical, but are almost identical to the original biologic.

to receive an expensive drug or its bio-similar, which would otherwise have cost him thousands of Indian Rupees.³¹ *B* placed his trust in the investigator and the hospital where the study was going to be conducted.

Both *A* and *B* had different factors motivating them to join the trials. Both derived monetary benefit out of the situation and both were led through an informative consent procedure. I concede that my sample size is limited and the situation of *A* and *B* might not be representative of the experiences of most of the trial participants in India, but given these participants' perceptions, I will proceed to analyse the implications of these two cases.

In the cases of *A* and *B*, the decision to participate in the trial was affected by either monetary or health incentives, or both. Does this mean that their consent should be deemed non-voluntary, hence, invalid? Should monetary or medical incentives for participation in trials be considered as coercive offers that invalidate consent? If we go by the provision on free consent in the law of contracts in India,³² an act is voluntary if there is no evidence of undue influence or coercion. If an act is driven or motivated by a person's values and preferences or the person's "*circumstance*, such as poverty, illness, or, in medical cases, the lack of "alternative treatment options",³³ the act is neither legally involuntary nor invalid. However, ethicists have argued this subject matter at great length. Some suggest that any amount of payment³⁴ cannot be termed as a coercive offer³⁵ and payment for

³¹ 100,000 INR = One Lakh Indian Rupees = 1232 GBP (approximately), cost of a single dose which is above the income threshold of the median per capita income in the country (which means half the population earns that amount in a year)

³² *Supra* note 22, Indian Contract Act, 1872.

³³ Wertheimer (2012), *supra* note 16.

³⁴ Payment here does not mean payment for services since trial participation is not viewed as rendering a service yet. Payment here means monetary or medical benefits that accrue during the course of participation. These monetary incentives are given to appear for trial screenings, for compensation of time or wages accrued due to trial participation, etc.

³⁵ There is a debate in philosophy and legal theory about what constitutes a 'coercive offer'. Coercive offers limit consent, as they are offers made to a person that tend to affect her options in a way that she has 'no choice' but to comply or else suffer an unacceptable consequence. According to Wertheimer and Miller, *genuine offers do not coerce* and even according to the Belmont Report coercion must include some kind of 'threat' which is absent in payment for research participation. See further A. Wertheimer & F. G. Miller, *Payment for Research Participation: A coercive offer?*, JOURNAL OF MEDICAL ETHICS, Vol. 34, Issue No. 5, (2008); *supra* note 1, the Belmont Report, (1979).

participation cannot invalidate consent.³⁶ Some suggest that large enough inducements of payments, which lead people into taking risks that they would otherwise not have taken, is undue inducement/influence.³⁷ Wertheimer claims that offers of payment that would compromise the validity of consent would be offers that distort a subject's capacity to assess the benefits and risks of participation. He further defines undue influence as an influence that is likely to make trial participants overestimate the benefits of participation or underestimate the risks. Wertheimer states that there is no undue influence when research subjects are capable of making rational appraisals of benefits and risks to reach the conclusion that participation in a trial or study is their best option.³⁸ Given these debates, some authors suggest that ethicists need to stop talking about undue inducement in reasonably risky³⁹ trials that are approved by independent reviews and focus on what they view as being *real* ethical concerns.⁴⁰ The following section will look at how the stakeholders understand this concern within their respective roles.

6.1.2. Do the stakeholders involved in realising informed consent in India think of undue inducement as a real ethical concern?

A clinician working for a pharmaceutical corporation told me that ethical guidelines indirectly depict economically poor trial participants as “lacking any form of agency which is quite paternalistic by itself”. The clinician said that in *some* trials, the majority of voluntary participation comes from economically and socially vulnerable groups because they get monetary or other incentives out of it. However, in his view, he said that in a country like India it was “not an unfair deal”.

³⁶ See P. McNeill, *Paying People to Participate in Research: Why Not?*, *Bioethics*, Vol. 11, (1997), pp. 390–396; T. L. Beauchamp, et al., *Pharmaceutical Research Involving the Homeless*, in: M. A. Grodin & L. H. Glantz, (Eds.), *CHILDREN AS RESEARCH SUBJECTS: SCIENCE, ETHICS, AND LAW*, (New York: Oxford University Press, 1994), pp. 193–214; *see also* Wertheimer (2012), *supra* note 16.

³⁷ R. Macklin, *'Due' and 'Undue' Inducements: On Passing Money to Research Subjects*, *IRB: ETHICS & HUMAN RESEARCH*, Vol. 3, Issue No. 5, (1981), pp. 1–6.

³⁸ A. Wertheimer, *Voluntary consent: Why a value-neutral concept won't work*, *JOURNAL OF MEDICINE & PHILOSOPHY*, Vol. 37, (2012), pp. 226–254.

³⁹ Meaning not excessively painful, risky and dangerous trials.

⁴⁰ E. J. Emanuel, *Ending Concerns about undue inducement*, *JOURNAL OF LAW, MEDICINE AND ETHICS*, Vol. 32, (2004), pp. 100–105.

I interviewed some NGO members working on clinical trial issues who alleged that trial sponsors, investigators and CROs frequently target poor population groups to conduct trials. Such accounts also appear in empirical studies conducted by other scholars in other countries.⁴¹ An NGO member I spoke to alleged that the CROs offered large sums of money to poor people to make them appear for trials. I asked a CRO member if the amount they gave to volunteers, especially economically vulnerable participants, to appear for screenings could be termed as ‘undue inducement’. The CRO employee said:

It is hypocritical to call the compensation rate large and undue inducement; if the money was less the same people would call it exploitation.

Let us consider this: if treated as a payment for labour or as a contractual job of a kind,⁴² there is nothing inherently unethical about paying research participants for participation in a trial. If it is about the degree of risk involved in the job, ethicists argue that it ought to be treated as no different to financial payment made to police, military, fire fighters or sanitation workers.⁴³ Moreover, the view of the clinician about paternalism is in line with the views of some authors on the subject of pervading paternalism in research ethics.⁴⁴ Although most of this paternalism is justifiable, some scholars argue that ethics committees can show unjustifiable paternalism by rejecting research that poses risk to people who are perfectly competent to decide for themselves.⁴⁵ In both the cases of *A* and *B*, the individuals

⁴¹ See S. SHAH, *THE BODY HUNTERS: TESTING NEW DRUGS ON THE WORLD’S POOREST PATIENTS*, (New Press, March, 2012); A. PETRYNA, *WHEN EXPERIMENTS TRAVEL: CLINICAL TRIALS AND THE GLOBAL SEARCH FOR HUMAN SUBJECTS*, (Princeton University Press, 2009); J. A. Fisher, “*Ready-to-Recruit*” or “*Ready-to-Consent*” Populations?: *Informed Consent and the Limits of Subject Autonomy*, *QUALITATIVE INQUIRY*, Vol. 13, Issue No. 6, (September, 2007), pp. 875–894.

⁴² For more arguments on why it is prudent to redefine the clinical trial field as an industry that employs labour and remunerates participants instead of giving them benefits, especially in low-resource settings, see generally A. H. KELLY & P. W. GEISLER (EDS.), *THE VALUE OF TRANSNATIONAL MEDICAL RESEARCH: LABOUR, PARTICIPATION AND CARE*, (Routledge, 2013).

⁴³ Wertheimer & Miller (2008), *supra* note 34.

⁴⁴ F. G. Miller & A. Wertheimer, *Facing up to Paternalism in Research Ethics*, *THE HASTINGS CENTER REPORT*, Vol. 37, Issue No. 3, (May-June., 2007), pp. 24–34. Although the authors clarify that this form of paternalism is justifiable, but they advance the view that research ethics are inherently paternalistic because bioethicists often ignore this inherently paternalistic nature of research ethics and ignore to set limits on the paternalism.

⁴⁵ S. J. L. Edwards, et al., *Research Ethics Committees and Paternalism*, *JOURNAL OF MEDICAL ETHICS*, Vol. 30, (2004), pp. 88–91.

seemed to have made a voluntary choice and appeared to be acting in their own best interest. It is then quite paternalistic to write about protecting them, “against their will, from the harmful consequences even of their fully voluntary choices and undertakings”.⁴⁶ If any systematised form of ethics, like ethics of clinical trials, imposes its own values and judgments on people “for their own good”, it seems well labelled as “paternalism”. In most cases, this kind of paternalism can be justified, especially when there is an unhealthy risk-benefit assessment negatively affecting the trial participant. Nevertheless, in other cases, we must be able to justify this kind of paternalism where we consider voluntary acts of people as “against their better judgement”.⁴⁷

We must also be cautious and consider the fact that there is a dearth of pan-India empirical data related to the economic and social backgrounds of trial participants. It would be a mistake to generalise such claims that *only the poor* or people with weak bargaining power are targeted for trial recruitment in countries like India. It is a natural assumption that people in need of money or health care would be more willing to participate in paid or otherwise beneficial clinical research studies. It is a reasonable assumption considering the vast socio-economic disparities that exist in India. But unless there are reliable statistics on the backgrounds of *all* trial participants, we must be cautious and avoid making blanket claims that they are *the only* groups that are recruited for *all* kinds of clinical trials being done in India.

I interviewed a doctor who had served on numerous Ethics Committees (ECs) that reviewed research protocols. He told me that the amount of payment or incentives given to trial participants needs to be disclosed in the study protocol for ethical review. He said that the point of ‘undue inducement’ was never raised as a problem in any of the trial studies that he had reviewed. He said that reviewers were mostly concerned with how risky the study/trial would be to the health of the trial participant and whether all measures would be taken to keep the trial participants safe. This corresponds with the most important aim of research ethics, which is participant safety. From a practical lens, EC members are not present during

⁴⁶ J. FEINBERG, HARM TO SELF (THE MORAL LIMITS TO CRIMINAL LAW), (New York: Oxford University Press, 1986), p. 12.

⁴⁷ ICMR Guidelines, *supra* note 25,

participant recruitment; as such, they cannot be expected to ascertain what amount of monetary or medical incentive would amount to undue inducement as ascertaining this would require detailed information and analysis of the economic or social background of each trial participant. With the limited time that they have to produce valid results for the study, they claim to prioritise issues that might compromise the health and safety of trial participants.

Some commentators consider inducement as ethically problematic only when it distorts the judgment of the agent, but if it does not distort the judgment and serves as a mere motivating factor then they claim it to be unproblematic for the validity of consent.⁴⁸ If we ascribe to this view, as long as a trial participant shows willingness to participate in a trial, then irrespective of the motivation of joining the trial, the autonomous decision making capacity of the individual needs to be respected. However, sometimes the willingness to participate is questioned when the participant comes from a disadvantaged background as people assume that poverty compromises the agency to such an extent that it leaves a person with no agency. Here I will revisit the concept of coercion from Chapter 3 to discuss my findings within the theoretical framework outlined therein.

6.1.3. Coercion or harsh choice circumstances?

The two major infractions on *voluntariness* are undue influence and coercion. We have dealt with undue influence in terms of inducement; let us now analyse situations that have been considered as coercive circumstances or circumstances that might act as undue influence on the decision-making capacity of the participants. George J. Annas, a prominent bioethicist, was once quoted as saying:

I'd argue you can't do studies ethically in a country where there is no basic health care. You can tell a person there that this is research, but they hear they have a chance to get care or else refuse their only good

⁴⁸ The IRB Guidebook mentions that an offer could be problematic if it is so attractive that it “may blind prospective subjects to the risks or impair their ability to exercise proper judgment” about the risks of participation in research, hence, according to Wertheimer & Miller (2007) distortion of judgment is the key, *supra* note 34. *See also* Office for Human Research Protections, Institutional Review Board: Guidebook, United States Department of Health and Human Services, available at <https://www.hhs.gov/ohrp/education-and-outreach/archived-materials/index.html> (last accessed on June 2, 2018)

chance at care. How can you put them in that position and then say they are giving informed consent?⁴⁹

Annas' use of "you put them in that position" reflects that he considers the situation of poverty or lack of basic health care as a coercive circumstance. As mentioned in Chapter 3, some scholars have suggested that there needs to be a distinction between *hard choice/harsh circumstances* and *coercion*.⁵⁰ It is sometimes assumed that when people have to make choices between a harsh set of circumstances, their choice is somehow coerced. This is assumed even when the agent makes the choice independently and in his/her own interest.

Philosophers have given different theories of coercion. I ascribe to the theory where philosophers have required coercion to have two elements – i) a set of choices available to the agent and ii) actions of external parties that have affected that set of choices.⁵¹ The second element seems to be missing from the situation described by Annas. The situation in developing countries like India is already one in which harsh circumstances (e.g. poverty or lack of basic health care) exist abundantly. There is hardly any evidence showing that the actions of parties conducting trials in developing countries unfairly create or affect those set of choices. The trial sponsors do not create the situations of injustice that already exist. They make attractive offers that might seem opportunistic considering the harsh circumstances that exist in parts of these countries, but those offers are not coercive.⁵² Moreover, such attractive offers are made in developed countries as well; especially where a participant

⁴⁹ S. LaFraniere, et al., *The Dilemma: Submit or Suffer* (Article 3 of *The Body Hunters*), WASHINGTON POST, (December 19, 2000).

⁵⁰ B. Campbell, *Informed Consent in Developing Countries: Myth or Reality?*, available at https://www.dartmouth.edu/~ethics/docs/Campbell_informedconsent.pdf (last accessed on June 2, 2018)

⁵¹ Based on Zimmerman's work on coercion and coercive wage offers See D. Zimmerman, *Coercive Wage Offers*, PHILOSOPHY AND PUBLIC AFFAIRS, Vol. 10, pp. 121–145; J. S. HAWKINS & E. J. EMANUEL, *EXPLOITATION AND DEVELOPING COUNTRIES: THE ETHICS OF CLINICAL RESEARCH*, (Princeton University Press, 2008), p. 25.

⁵² *Id.* See also *supra* note 34, Wertheimer & Miller (2007) where the authors argue that 'having no reasonable alternative' might naturally be viewed as a necessary condition for coercion, which it is, but not all offers where people have no reasonable alternatives leads to coercion, as there are no *threats* involved. Similarly, the authors anecdotally argue that the need for money does not preclude voluntary consent and debunk the claims of authors like McGregor who suggest that taking advantage of someone's vulnerability would be coercive. See J. McGregor, "*Undue inducement*" as *coercive offers*, AMERICAN JOURNAL OF BIOETHICS, Vol. 5, Issue No. 5, 2005; pp. 24–5.

suffering from a disease with no cure has a limited set of options from which to choose. Hence, hard choice circumstances need to be distinguished from coercion. One clinician based out of Mumbai, while talking to me about ‘guinea-pig’ coverage in the media and about poor people having no choice but to participate in trials, said:

I think there is a big misconception that poor people have no other choice than to participate in trials in India. They have multiple options for getting healthcare. If money is an issue, they even have extremely subsidised government hospitals where they can get treatment for next to nothing. Yes! the lines are big, but people all over the country middle class, even the rich, and the poor, all suffer in long queues. Why would a person just volunteer for a trial because they have no other choice and no choice for what? This [while air quoting] “no other choice” business makes absolutely no sense to me. There is always a choice and we don’t force them to do anything...Even if money is the reason for them to participate then how is it any different from *maut ka kuan* [the well of death motordrome] at the circus? Don’t they risk their life for nothing but money there? So you see at least in clinical research, even if there is a risk, the benefit goes to thousands of other people.

Scholars have argued extensively over whether harsh circumstances affect people’s autonomy,⁵³ this, however, does not lead to the conclusion that harsh circumstances invalidate consent. I address this point further in Chapter 7. The real problem lies not in the debate on whether poverty invalidates consent, but in the *existence* of harsh circumstances in developing countries that *might* induce people to choose clinical trial participation for any form of benefit that they are otherwise denied. Stakeholders seemed to think that the focus should shift from mere theoretical debates in clinical research to finding real solutions to eliminate these harsh circumstances. As a member of one of the higher regulatory bodies, who requested strict confidentiality, opined that academics will be taken more seriously if they provided real solutions, he said:

⁵³ J. A. Fisher (2007), *supra* note 40, saying that such circumstances affect an agent’s autonomous decision making abilities, at p. 889. Other authors have argued that poverty affects individual autonomy as it limits individual’s life plans and choices. See S. K. VAUGHAN, POVERTY, JUSTICE, AND WESTERN POLITICAL THOUGHT, (Lexington, 2009), p. 7; E. S. Azevedo, *Decisions in Circumstances of Poverty*, EUBIOS JOURNAL OF ASIAN AND INTERNATIONAL BIOETHICS, VOL. 12 (2002), pp. 105-107. Others like Campbell, Hawkins, and Emanuel have rejected the proposition that harsh circumstances affects people’s choice, though they agree that harsh circumstances limit their choice set. B. Campbell *supra* note 48; HAWKINS AND EMANUEL (2008), *supra* note 49.

...people sitting in plush offices [of Universities] tell us how we do everything wrong, they use big fancy words for simple common sense things....If they [academics] have real data-based solutions, we respect them and we ask for help. These [policy] decisions take months and years of deliberations. They are made keeping in mind needs of the most number of people. If some benefit in money terms or medically from trials why should we not let them?

This shows that harsh circumstances are neither a serious concern for practitioners/researchers nor for regulators, yet they are the focal point of discussions in academic literature about ethics of clinical research in developing countries.

In the next section I look at another important facet of voluntariness that has not yet been mentioned, i.e., the right to withdraw from a trial at any time. This important right is arguably responsible for taking away the contractual element from a consent agreement, since it means that the research participant is immune from performing her contractual obligations. Here we shall see how different stakeholders perceive this right and what we can learn from this.

6.1.4. The right to withdraw: completing voluntariness

Participants, even those that are given inducements for participation, are free to withdraw their participation at any point, even where it jeopardises the trial. The right to withdraw from trial participation at any time completes the voluntariness condition of a trial.⁵⁴ Some trials conducted in India have poor retention rates and a high rate of dropouts. One scientist at CDRI said:

...we [sic] need to realise that the clinical trial process is an extremely slow one and the first few interactions with the participants is [sic] quite cumbersome...here [at CDRI] the rate of drop outs from trials is about 10-15% which is higher than the fewer number of drop-outs elsewhere in the world. These are not unusual figures for us.

This shows that perhaps the agency of trial participants in India is not as reduced as some claim it is. An investigator, based at a private hospital in New Delhi, claimed that poor participant retention was a good example of participants not being bound to the trials as they were free to leave the study according to their wishes. However, one

⁵⁴ S. J. L. Edwards, *Research Participation and the Right to Withdraw*, BIOETHICS, Vol. 19, Issue no. 2, (2005), pp. 112-130

public health activist refuted the claim. According to the activist, participant retention was “not an indicator” of unproblematic informed consent procedures. Another public health activist agreed with his colleague and said:

Most trial participants fear leaving trial studies as that affects their relationship with their care provider and no one wants to take a study drug and leave the study without the follow-up supervision.

This concern is supported by a study conducted by Mandava and colleagues suggesting that participants from developing countries were less likely than those from developed countries to be willing to refuse to join or withdraw from a trial.⁵⁵ This was, the study found, because participants in developing countries were more likely to be concerned about the consequences of refusal or withdrawal, for instance, being refused health care. There appears to be a division between different stakeholders as to how to interpret the relatively high drop-out rate, and on whether there is a high drop-out rate at all. But some global pharmaceutical company representatives reiterated views similar to those of the CDRI scientist, that the refusal rates for trial participation in India were sometimes more than the acceptance rates. They showed me their data charts on participation and refusal rates and the rate of refusal and drop outs in India were considerably higher than their trial sites in other countries. However, in most academic articles, dealing with clinical research in developing countries, researchers fail to mention that sometimes recruiters struggle to achieve trial participation and retention in countries like India. When asked about informed consent procedures in general, a representative of a global pharmaceutical MNC, who was also a clinical trial site manager in India, said:

The informed consent procedure is very robust. There is a healthy refusal rate of participants; the investigators are thoroughly trained. In fact, it is a struggle to recruit patients sometimes, because their opinions are respected.

Existing empirical studies show that factors contributing to dropouts include fear of serious and adverse effects, change in trial participant’s residence, poor compliance with study protocol, participant’s fear of side effects, and a fear for study

⁵⁵ A. Mandava, et al., *The quality of informed consent: Mapping the landscape: A review of empirical data from developing and developed countries*, JOURNAL OF MEDICAL ETHICS, Vol. 38, (2012), pp. 356 -365.

procedures.⁵⁶ This is in contrast to the allegation by the activist above that participants fear dropping out of trials.

The right to withdraw from a trial is an important precondition of *voluntariness*.⁵⁷ This right seems to have been respected in the studies that were conducted by my interviewees because they claimed that their dropout rates were high, and if their claims are true (which I cannot confirm as the data charts were shown but not shared with me) it shows that the agency of the research participants was respected.

The next section will look at a meta-analytical study that analyses several other empirical studies to determine what motivates people in India to participate in or drop out of trials. This study will help us understand that the reasons people participate in trials in India are not simple.

6.1.5. What motivates people in India to participate in (or drop out from) trials?

There are multiple empirical studies on what prompts people to become, or drop out as, trial participants in India.⁵⁸ Shah and colleagues conducted a meta-analytical study that evaluated all empirical studies (up until 2010) that determined the factors contributing to decisions made by trial participants in India. The variables of this study are given in Appendix II. In the analysis, the following results factored in:⁵⁹

⁵⁶ See R. A. Kadam, et al., *Challenges in recruitment and retention of clinical trial subjects*, PERSPECTIVES IN CLINICAL RESEARCH, Vol. 7, Issue No. 3, (July-September, 2016), pp. 137–143.

⁵⁷ Knowledge about the right to withdraw from a study has also been used to empirically assess and measure voluntariness in some studies, *see for example* P. A. Marshall, et al., *Voluntary Participation and Informed Consent to International Genetic Research*, AMERICAN JOURNAL OF PUBLIC HEALTH, Vol. 96, Issue No. 11, (November, 2006), pp. 1989-1995.

⁵⁸ See J. Y Shah, et al., *What Leads Indians to Participate in Clinical Trials? A Meta-Analysis of Qualitative Studies*, PLOS One, Vol. 5, Issue No. 5, (2010). This study conducted a meta-analysis of all relevant studies that aimed at evaluating the factors and barriers that contributed to participation in clinical trials from the perspective of Indian trial participants.

⁵⁹ *Id.* The study included the percentage of participants contributing to each of the theme. The authors determined the average for similar responses in each study after which they calculated the total of similar responses from all studies and reported it as a percentage. They used direct quotes and survey questionnaires to reach the percentages.

Factors favouring research participation⁶⁰

Personal health Benefits	Altruism	Methods for motivating participation (See Appendix II)	Source of extra income/benefits	Detailed knowledge about trials	Trust in Physicians
48%	43%	34%	31%	21%	8%

Factors acting as barriers to research participation⁶¹

Mistrust in trial organizations	Concerns about efficacy and safety of trials	Dependency Issues	Loss of Confidentiality, Privacy concerns	Trial burden	Psychological reasons	Language
26%	21%	19%	17%	11%	6%	1%

It is evident that although a substantial percentage of people considered participation in trials out of altruism (43% of sample size), the majority participated in them because of personal health benefits and as a source of additional income (48% and 31% respectively). There are clear overlaps in what factors motivated them to participate in trials; some might have had altruistic options combined with the motivation of gaining benefits. As noted in Section 5.1.1., irrespective of whether some ethicists approve or not, payment in the form of financial or monetary benefits is important for the recruitment for trials in India. The factors affecting drop-out rates or factors that lead to people not volunteering for trials includes a high percentage of people (about 26%) who mistrust trial organisations. This is interesting because it shows that money itself is not sufficient to entice people to participate in trials. About 21% of people would not participate in or would withdraw from trials because of concerns regarding the safety and efficacy of trials. This shows that a substantial number of people regard the trial industry in India with suspicion. Hence, recruitment for trials is not as effortless as most people think, even in resource-poor settings and where financial inducements are paid.

⁶⁰ *Supra* note 57, see Appendix II

⁶¹ *Id.*

The most striking feature of this study is the percentage of people who cited ‘language’ as a barrier to trial participation. A huge proportion of bioethical literature cites language as a major problem in realising informed consent in developing countries with multiple languages and high illiteracy rates like India.⁶² But only 1% of Indian people interviewed for these empirical studies regarded it as a barrier to trial participation. Moreover, the first table shows that the percentage of people who participated (or were willing to participate) because they received detailed information about the trial was about 21%. By inference, this means that for 79% of the people, detailed information about the trial was not a decisive factor in volunteering for a trial. This is important because information disclosure is the other major ethical requirement for proper informed consent procedure. The ethical and legal requirement also suggests communication of information to the trial participant in the language and manner most suitable to the understanding of the prospective trial participant. This takes us to the second ethical requirement of *full information disclosure* in clinical trials.

6.2. INFORMATION

Full information disclosure, along with assuring comprehension of that information is another major ethical and legal requirement for informed consent. It is a requirement by law and by the ethical guidelines in India that adequate information must be given to the trial participant in a “simple and easily understandable unambiguous language in a document known as the Informed Consent Form with Participant/Patient Information Sheet.”⁶³ For the sake of analysis, I am going to presume the precondition that general information is given during the recruitment of participants for a trial. The problem that is identified by numerous scholarly studies

⁶² Almost every piece written about informed consent in trials in developing countries mentions the language as a barrier to full comprehension of information. *See for example* S. Sanchez, et al., *Informed consent procedures: responsibilities of researchers in developing countries*, BIOETHICS, Vol. 15, Issue No. 5-6 (2001), pp. 398–412; YJML (Staff writers), *The Ethics of Pharmaceutical Testing in the Developing World*, THE YALE JOURNAL OF MEDICINE AND LAW BLOG, (December 9, 2013); D. M. Harris, *Autonomy and Informed Consent in Global Perspective*, in: D. M. HARRIS, *ETHICS IN HEALTH SERVICES AND POLICY: A GLOBAL APPROACH*, (Josey-Nass, Wiley Imprint, 2011); A. A. Hyder, et al., *Ethical review of health research: a perspective from developing country researchers*, JOURNAL OF MEDICAL ETHICS, Vol. 30, Issue No. 1, (2004).

⁶³ ICMR Guidelines, *supra* note 25, at p. 21; *see also supra* note 3.

is whether the trial participants adequately understand the information. Scholars have extensively written about poor literacy conditions in the developing world that make this ethical requirement a difficult condition to achieve.⁶⁴ Most other empirical studies in this field have been dedicated to suggesting methods through which participant comprehension of information in clinical trials can be improved. These include methods like making consent forms shorter and less technical, using teach-back methods, using bulleted fact sheets, Q&A sessions, person-to-person interaction or interaction with a study educator, use of locally relevant analogies, and so on.⁶⁵ The next section considers how the stakeholders view participant comprehension in India.

6.2.1. INFORMATION DISCLOSURE AND OBTAINING PARTICIPANT UNDERSTANDING IN ACTION

The problems of illiteracy noted above have represented a major challenge for recruitment in India. One scientist/investigator at the Central Drugs Research Institute (CDRI), a government funded clinical research institute, spoke about illiteracy as a challenge for recruitment for trials, the scientist said:

...illiteracy is a very big challenge while recruiting participants...extra care has to be taken...We try to mostly avoid recruiting completely

⁶⁴ D. J. Krogstad, et al., *Informed Consent in International Research: The Rationale for Different Approaches*, THE AMERICAN JOURNAL OF TROPICAL MEDICINE AND HYGIENE, Vol. 83, Issue No. 4, (October, 2010), pp. 743-747; M. Alaei, et al., *Obtaining Informed Consent in an Illiterate Population*, MIDDLE EAST JOURNAL OF DIGESTIVE DISEASES, Vol. 5, Issue No. 1, (January 2013), pp. 37-40; M. O. Afolabi, et al., *Informed Consent and Comprehension in African Research Setting*, TROPICAL MEDICINE AND INTERNATIONAL HEALTH, Vol. 19, Issue No.6, (June, 2014), pp. 625-642; L. H. Chaisson, et al., *Repeated Assessments of Informed Consent Comprehension among HIV-Infected Participants of a Three-Year Clinical Trial in Botswana*, PLOS ONE, Vol. 6, Issue, No. 10, (October 2011).

⁶⁵ See for example A. L. Corneli, et al., *Improving Participant Understanding of Informed Consent in an HIV-Prevention Clinical Trial: A Comparison of Methods*, AIDS BEHAVIOUR, Vol. 16, Issue No.2, (February, 2012), pp. 412-421; W. Montalvo, *Participant Comprehension of Research for Which They Volunteer: A Systematic Review*, JOURNAL OF NURSING SCHOLARSHIP, Vol. 46, Issue No. 6, (August, 2014); E. Cohn & E. Larson, *Improving Participant Comprehension in the Informed Consent Process*, JOURNAL OF NURSING SCHOLARSHIP, Vol. 39, Issue 3, (August 2007); N. E. Kass, et al., *A pilot study of simple interventions to improve informed consent in clinical research: Feasibility, approach, and results*, CLINICAL TRIALS, Vol. 12, Issue No. 1, (2015), pp. 54-66; J. Flory & E. Emanuel, *Interventions to improve research participants' understanding in informed consent for research: A systematic review*, JOURNAL OF AMERICAN MEDICAL ASSOCIATION, Vol. 292, (2004), pp. 1593-1601.

illiterate people for trials. In our experience most volunteers have been well-informed and educated...they even question the consent forms and ask lots of questions...the patient information sheet [PIS] is always printed out in local languages and explained in detail...we put major efforts while recruiting participants...having a non-informed trial participant is difficult even for a trial to be conducted properly.

Two important points can be inferred from the experience of this scientist from CDRI. First, the motivation to take consent here is not to act ethically but efficiency i.e., getting the trial to work well. Second, it might be easier to refrain from recruiting illiterate participants for research altogether. However, the CDRI scientist noted that even educated trial participants could have difficulty understanding the exact nature of the trial because the terms can be too technical. He said that their approach in the consent counselling sessions is to make the information as simple as possible and to let participants ask as many questions as they want.

Perhaps in the effort to live up to the highest ethical standards it might seem practical to avoid recruiting trial participants who are illiterate or might have difficulty understanding the nature of a trial study. However, are we then not assuming the patronising stance that illiterate people cannot be made to understand complex information? A researcher from India addressed this point:

...[n]ote that while potential research participants from the lower classes may be illiterate, they are not ‘uneducated’. Individuals often have life experiences which empower them. A researcher must be innovative in creating a consent process for communicating information which ensures that potential research participants understand the purpose of the research before consenting.⁶⁶

Debates related to trials in developing countries have not yet reached a point where parties demand that certain poor and illiterate populations be excluded from being recruited for trials altogether. However, allegations of “recruiting and exploiting poor and illiterate people” made against CROs in India⁶⁷ led some CROs to adopt policies

⁶⁶ A. Bhan, et al., *Informed Consent in International Research: Perspectives from India, Iran and Nigeria*, MEDICAL ETHICS, Vol. 3, Issue No. 1, (2006).

⁶⁷ V. Sundaram, *U.S. Pharmaceutical Companies Testing Drugs on India’s Poor*, NEW AMERICA MEDIA, (August 1, 2011); S. Verma, *Trial and Error*, THE TELEGRAPH, (October, 14, 2012); A. Sengupta, *Parliamentary Committee Indicts Clinical Trial Industry*, DELHI SCIENCE FORUM, (September 12, 2013); M. Politzer & V. Krishnan, *The dark underbelly of India’s clinical trials business*, LIVEMINT, (October 12, 2012).

of excluding illiterate people from trial recruitment completely.⁶⁸ A CRO I spoke to based out of Andhra Pradesh confirmed that they had decided to not recruit illiterate participants and had been following the policy since the year 2014. Nevertheless, it is unlikely that such policies of non-recruitment of illiterate people will be expanded in the near future. Instead, what the field arguably needs is more context specific, innovative, and practical solutions to practical problems like assuring adequate understanding of information. As an investigator/scientist at a public hospital said:

These things are obvious. When people don't have the capacity to understand you make them understand using simple words...You don't need a law to tell you that you have to do that. It is [a] basic way of communication.

The experiences of these practitioners show that though obtaining reasonable comprehension of trial information from the participants can be difficult, it is not impossible. It requires the right approach towards the consent process. The approach seems to be simple: you use the language the participant is most comfortable in and you simplify the information to convey the risks and the purpose of the study most efficiently. The purpose behind adopting such an approach should be to ensure that the trial participants make an informed choice. Such an approach is beneficial to both the parties because having ill-informed trial participants could be harmful to the trial process and could compromise the results of the trial study. We must remember that communication between the investigator and the trial participant is not a one-off process and instead involves months or years of interaction. This is because a trial lasts for several months, and sometimes several years, and if the participant decides not to drop out of the trial in the middle of such trial period, the interactions are frequent. Therefore, it does neither party any good to be complacent about 'adequacy and understanding' of the information during the consent process.

In action, as we have seen from the study conducted by Shah and colleagues above, there are many more factors affecting a trial participant's motivation to join a trial than mere adequacy of information. If we go back to the cases of trial

⁶⁸ Clinical research Society Report, *Illiterate persons not to be used for clinical trials*, available at <http://www.clinicalresearchsociety.org/illiterate-persons-not-to-be-used-for-clinical-trials/> (last accessed on June 2, 2018)

participants in Section 5.1.1., it is quite apparent that *A* did not care much about information related to the trial. He was of the opinion that BA/BE studies are low-risk, but even if they were high risk, he would have joined the study anyway. His consent was pre-determined to such an extent that any other information given to him at the consent process would not matter much. In *B*'s case, extreme trust in the institution and the investigator, along with the health and monetary benefit, overrode any need for detailed information. Although from what *B* said, it seems that he understood the concept of randomisation in trial, even if he did not know the clinical jargon. The relevant point here is that even if there are other factors motivating trial participants to join trials than mere adequacy of information (as the study suggested in Section 5.1.5), it is the duty of the investigator to ensure that the information is comprehensible and that the participant has understood the information. Only when there is satisfactory comprehension of information can we call informed consent meaningful; otherwise, its significance is reduced to a mere procedural requirement. This raises the question - how does one assess satisfactory comprehension of information as an investigator of a trial?

Most investigators I interviewed felt that they had duly complied with all the necessary requirements of informed consent once they had informed the participant and taken written consent. But when asked if they had ascertained that the participant had understood the information, some investigators were not exactly sure about how such an assessment could be made. As one investigator said:

We ask again and again if they have understood what a technical term means or what is required of them. They ask us questions and we answer, isn't that enough? Should we take written tests? *Itna time nahi hota* [we do not have so much time]. Some people opt to bring their more educated children or relatives to explain them some things. We allow even that...I think it is not possible to guarantee or exactly tell about things like comprehension. [sic]

Taking note of the difficulties in assessing comprehension of trial participants, some empirical studies in the US have found that repeated participant consent counselling sessions help improve comprehension of information.⁶⁹ Some researchers have

⁶⁹ D. A. Wirshing, *Informed Consent: Assessment of Comprehension*, THE AMERICAN JOURNAL OF PSYCHIATRY, Vol. 155, Issue No. 11, (November 1998), pp. 1508-1511. In this study, during the

suggested repeated use of questionnaires within an interval of a few days to assess comprehension⁷⁰ and others have devised their own comprehension tests suitable to their field of study to assess participant comprehension, such as the Deaconess Informed Consent Comprehension Test (DICCT).⁷¹ Participant comprehension can thus be assessed in a number of ways.⁷² It can safely be concluded that eventually it is up to the will and effort of the individual investigator and the intent of the trial sponsor to ensure that there is sufficient comprehension of information by trial participants of their study. Of course, the other option could be to legally necessitate ‘comprehension assessment’ as part of the consent process, but for that, we would first need some agreement on the best possible method to assess comprehension. The next section will look at the legal understanding of this essential requirement of informed consent.

6.2.2. Law and its understanding of the condition of full disclosure of information

We have seen that the focus of most ethical and empirical studies in this area has been on the *understanding* of information by the trial participant. Let us now see how

consent counselling sessions, the consent forms were read and explained to 49 patients suffering from schizophrenia. These patients, who were participating in an ongoing trial, had to answer a questionnaire relating to each research protocol. The protocol procedures were repeated in every session until the patients answered 100% of the questions correctly. Seven days later when the subjects were asked the same questions to ascertain how much of the information they had retained; there was 80% data retention. It was analysed that about 53% of the patients required a second trial of the questionnaire, and 37% of the participants required three or more trials to achieve 100% correct responses.

⁷⁰ Chaisson, et al., (2011), *supra* note 63, these sessions included “using a 20-question true/false quiz administered in 6-month intervals” within the context of a randomized placebo-controlled trial for the prevention of tuberculosis amongst HIV-infected adults in Botswana, the trial was conducted between the years 2004-2009.

⁷¹ C. K. Miller, et al., *The Deaconess Informed Consent Comprehension Test: An Assessment Tool for Clinical Research Subjects*, Vol. 16, Issue No. 5, PHARMACOTHERAPY, (September-October, 1996), pp. 872-878. This test was based on 36 year old, mostly female research subjects, who had undergone about two years of college, this test may not be valid for different subjects with completely different demographics, but more variations of this can be made. This test is a 14-item generic comprehension test, it is written at the reading level of eighth grade and requires 12 minutes to administer and score.

⁷² Although each set of instrument to assess comprehension comes with its own set of limitations like lack of generalisability and absence of details outlining how test results ought to be used to guide clinical decision-making. See L. D. Buccini, et al., *Assessing Clinical Trial Informed Consent Comprehension in Non-Cognitively-Impaired Adults: A Systematic Review of Instruments*, Vol 5, Issue No. 1, (2009).

the law deals with this requirement. Schedule Y of the Indian Drugs and Cosmetics Act, 1940, mentions that the information should be presented in a non-technical and understandable manner, but the provision is laid down as a guideline without a remedial clause. But as we saw in chapter 4, in case law related to informed consent in treatment there is a preoccupation with outlining what *adequate* information disclosure might mean and according to whom. Previous chapters have highlighted the fact that courts in different jurisdictions determine the disclosure of adequate information according to three standards: 1) the professional practice standard; 2) the reasonable person standard; and sometimes 3) the subjective patient standard. As has been discussed in Chapter 4, the Indian courts follow the professional practice standard.⁷³ In that chapter, I also suggested that the reasonable person or the subjective standard would be the best approach to protecting the autonomy of the trial participant in cases arising out of lack of informed consent in research. However, such a standard would also require the courts to assess the *materiality* of the information to be disclosed.

The medical professionals must divulge all ‘material risks’ to the patient for the duty of information disclosure to be fulfilled.⁷⁴ Prior to the evolution of the reasonable person standard, the disclosure of material risk was looked at from the viewpoint of the established medical professional standard. Now most courts (in

⁷³ The most recent Supreme Court case that laid down the difference between real and informed consent and gave reasons as to why the Bolam test shall apply to information disclosure cases in India, see *Samira Kohli v. Dr. Prabha Manchanda and Another*, (2008) 2 SCC 1.

⁷⁴ In the *Canterbury* case from the USA, [*Canterbury v. Spence* (464 F.2d. 772, 782 D.C. Cir. 1972)], it was held that risk is material “when a reasonable person, in what the physician knows or should know to be the patient's position, would be likely to attach significance to the risk or cluster of risks in deciding whether or not to forego the proposed therapy”. In English law, Lord Scarman’s dissenting view in *Sidaway* case, [*Sidaway v. Board of Governors of the Bethlem Royal Hospital* [1985] AC 871], laid out what test of materiality ought to be, he said, “I think that English Law must recognise a duty of the doctor to warn his patient of risk inherent in the treatment he is proposing...The critical limitation of is that the duty is confined to material risk...The test of materiality is whether in the circumstances...the court is satisfied that a reasonable person in the patient’s position would be likely to attach significance to the risk”. Lord Scarman’s view was upheld by the UK Supreme Court quite recently in *Montgomery v. Lanarkshire Health Board*; (2015) UKSC 11. The Court held, “the test of materiality is whether, in the circumstances of the particular case, a reasonable person in the patient’s position would be likely to attach significance to the risk, or the doctor is or should reasonably be aware that the particular patient would be likely to attach significance to it.” See also J. Miola, *On the Materiality of Risk, Paper Tigers and Panaceas*, MEDICAL LAW REVIEW, Vol. 17, (Spring 2009), pp. 76–108.

common law jurisdictions) look at materiality from the point of view of whether a reasonable person in the patient's position would be likely to attach significance to the risk.⁷⁵ However, we must question what *materiality* means in the modern world, where access to information is easier, and where decision-making is not the same as it used to be. Some, like Sawicki, say that weighing up the risks and benefits of the various treatment alternatives does not accurately reflect modern understandings of how patients make medical decisions.⁷⁶ She holds the view that existing common law disclosure duties fail to capture multiple non-medical factors that are relevant to patients. Such non-medical factors include the cost of treatment, the physician's personal characteristics, the social implications of health care interventions, and the legal consequences associated with diagnosis and treatment.⁷⁷ Hence, she seeks to expand the doctrine of informed consent to include information that may be relevant to patients/participants but falls outside the traditional scope of materiality as understood in medicine and law. I agree with this to the extent that there are multiple factors that affect how modern patients and trial participants make decisions pertaining to their bodies these days. However, the common law has usually limited the scope of disclosure to medically material facts and any argument favouring an extended scope would have to be thoroughly examined,⁷⁸ a task that is beyond the scope of this thesis.

Nevertheless, in addition to disagreements over what constitutes materiality in disclosure there is the added problem of risks in the case of clinical trials. This is because some of the risks are discovered while the drug is in the process of being tested upon the trial participant. Therefore, the uncertainty of risks, including every

⁷⁵ *Id.*

⁷⁶ N. N. Sawicki, *Modernizing Informed Consent: Expanding the Boundaries of Materiality*, UNIVERSITY OF ILLINOIS LAW REVIEW, Vol. 1, (2016), pp. 821–871

⁷⁷ For instance, a Texas court faced a case where a psychiatrist was sued for civil damages based on his testimony in a criminal case and for his failure to advise his patient that he might testify against him to prove his diagnosis. *See Clark v. Grigson*, 579 S.W.2d 263 (Tex. Civ. App. 1978). In another case, the Colorado Appellate Court dismissed a claim where the deceased patient's wife claimed that the physician's misdiagnosis caused the patient to cancel his life insurance policy and they suffered heavy monetary damages due to the action. These cases show that there are often legal consequences to diagnosis that are kept outside the material facts for information disclosure. *See In re Estate of Blacher*, 857 P.2d 566 (Colo. App. 1993).

⁷⁸ For normative arguments in favour of the said position, *see* Sawicki (2016), *supra* note 75.

other material information that has the potential to affect a participant's decision to join the trial, must be fully disclosed by the investigator. Most investigators I interviewed claimed to be doing just that. Some investigators even showed me consent forms where the study protocol had been explained in different languages and the risks were outlined in a bullet point format. I could not get a copy of those forms as they were forms of ongoing trials, but I have attached a *similar* copy of a trial consent form from a sample trial (in English and Hindi) in Appendix III. The language of the consent form is simple and there are about seven double-sided pages of information. In my estimation, a person has to be educated to at least high school level to be able to understand the form's content. Although a seven-page consent form is a reasonable sized form, one investigator showed me a 50-page consent form. When I asked the investigator how he translated such long and dense forms to people with low literacy levels, the investigator told me that he sat down with each participant and explained each bullet point of potential risk in detail. He said that his strategy worked well especially for people who could not read the consent form, although he claimed that he followed this procedure with every participant irrespective of his/her educational background. He said:

We try to make sure that the uncertainty about risks is conveyed as clearly as possible because we don't want legal suits and other problems because of that.

It might be obvious, but it does no harm to emphasise that while the potential threat of a lawsuit might change the attitude of some people regarding certain ethical requirements, it is not sufficient to make research ethical. There is much more to the process of a clinical trial than the prerequisite of ethical informed consent. While informed consent is *necessary* in all cases, in no case is it *sufficient* for ethical clinical research. There are other ethical benchmarks, like fair subject selection, value to society, risk benefit ratio, scientific validity of the research, collaborative partnerships between stakeholders, independent review of the study, and respect for the participants and study communities, that need to be reached in order to make

clinical research ethical.⁷⁹ But these benchmarks are outside the scope of informed consent, and hence excluded from discussion in this chapter.

However, regardless of the shifting academic debates, as for example in the case of materiality, the difference between the legal and ethical requirements for information disclosure remains the same. The ethical standard preoccupies itself not just with the adequacy of information, but also with the understanding of it. It not only takes into account the potential vulnerabilities (cognitive, emotional, etc.), but also the cultural, educational and language barriers that might make comprehension of information difficult. It focuses on effective communication and dialogue with the trial participant. In contrast, the legal standard has a limited remit because it focuses on the standards of disclosure and what leads to causation of injury rather than the format or the content of communication.⁸⁰ The legal standard that comes closest to corresponding with the ethical requirements is the subjective patient standard. However, it is not the dominant legal standard in the law of informed consent. The law has not yet evolved to fully embrace the ethical standards required to ensure comprehension of information to the patient/participant. This is a classic case where, despite progressive developments in case law, the law makes an uneasy compromise with ethical theory.

This discussion prompts another question – even if we assume that the information was adequate, non-technical, and communicated in an understandable manner, how do we assess that the trial participant has the capacity or competence to understand that information? The next section will assess considerations affecting the trial participant's capacity to give informed consent. It will highlight the practice of equating legal age of majority with capacity (even for trials not involving children).

6.3. COMPETENCE / CAPACITY

As noted above, it is not just the disclosure of information that is relevant; the research subject must also have the capacity to consent. Capacity to consent refers to

⁷⁹ E. J. Emanuel, et al., *What Makes Clinical Research Ethical?*, THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, Vol. 283, Issue No. 20, (2000), pp. 2701-2711.

⁸⁰ L. B. Andrews, *Informed consent statutes and the decision making process*, JOURNAL OF LEGAL MEDICINE, Vol. 5, Issue no. 2, (1984).

the decision-making competence of an individual. As noted in Chapter 4, informed consent is not just about the capacity to be able to enter into a contract; it is about the capacity to be able to make a decision after rationally understanding the information and the consequences of that decision. However, when I asked the investigators how they ascertained capacity of the trial participants, almost all of them told me that their trial participants were above 18 years of age. It is important to note that none of the investigators I interviewed were involved with trials on children, minors or people with mental illness. However, levelling capacity with age is a simplistic and legalistic way to approach the informed consent process.

When the principle of informed consent to treatment was being laid out in the US courts, it included “every human being of adult years and sound mind”.⁸¹ Adult years meant the age at which individuals were considered capable of making their own decisions. In India, the legal age of majority is 18 years of age, which means that it is the age at which an individual is considered to be of ‘adult years’.⁸² Schedule Y of the Drugs and Cosmetics Act, 1940, says that legally incapacitated persons, like minors or people with mental illness, would need the signature of a legal representative to become trial participants.⁸³ But the manner in which this legal requirement plays out, or has played out, in practice undermines the rationale behind this requirement. The next section will revisit the *HPV vaccine case*, which was a study conducted on minor girls. Although ethical issues involving children are outside the scope of this thesis, I am mentioning this case in the next section to show how the *simplistic* legal understanding of capacity is counterproductive and not sufficient to protect trial participants.

6.3.1. CAPACITY IN ACTION

One cannot argue against the importance of vaccine trials on children in India,⁸⁴ but the conduct of these trials has raised some grave ethical concerns. As was discussed

⁸¹ *Schloendorff v. Society of New York Hospital*, 105 N.E. 92 (N.Y. 1914).

⁸² Section 3, Indian Majority Act, 1875.

⁸³ *Supra* note 3.

⁸⁴ In a UNICEF report from 2015, around 1.2 million children in India were reported to have died of preventable causes, more than half of them were vaccine preventable cases. Which translates to about 17% of the world’s total under the age of 5 year deaths. As such, it becomes a public health need to

in the introductory chapter, in the *HPV vaccine case*, the Indian government documented ethical misconduct due to the death of seven minor girls enrolled in a clinical trial for the human papillomavirus (HPV) vaccine in the states of Andhra Pradesh and Gujarat. Although, after an enquiry, the deaths were found to be unrelated to the trial vaccine, the media coverage of the event led to a debate on the informed consent requirements for minors and their capacity to consent.⁸⁵ The Parliamentary Committee Report on the alleged irregularities in the HPV trial conducted by the NGO PATH revealed serious discrepancies in the informed consent process. The report found:

The Informed Consent document approved by various Ethics Committees on PATH project included the sentence: “I have read the information in this consent form (or it has been read to me). I consent to allow my daughter to receive three doses of HPV vaccines.” In the case of Andhra Pradesh 9,543 forms were signed, 1,948 had thumb impressions while hostel warden had signed 2,763 forms. In the case of Gujarat 6,217 forms were signed, 3,944 had thumb impressions and 545 were either signed or carried thumb impression of guardians. The data shows that a very large number of parents/guardians were illiterate and could not even sign in their local language i.e. Telugu or Gujarati.⁸⁶

The report found that the Andhra Pradesh State Government’s circular directing all Headmasters/Wardens in all private/government/ashram schools to sign the consent forms on behalf of parents/guardians was legally questionable. According to the rules under Schedule Y, in case the trial participant or his/her legal guardian (for minor or incapacitated person) is an illiterate person, an independent person has to sign the

start vaccination and immunisation programs that sometimes requires trying new drugs. See UNICEF, *The State of World’s Children Report 2016*, available at https://www.unicef.org/publications/files/UNICEF_SOWC_2016.pdf (last accessed on June 2, 2018); see also P. S. Kulkarni, *Current topics in research ethics in vaccine studies*, PERSPECTIVES IN CLINICAL RESEARCH, Vol. 4, Issue no. 1, (January – March, 2013).

⁸⁵ A. Buncombe & N. Lakhani, *Without consent: how drugs companies exploit Indian 'guinea pigs'*, THE INDEPENDENT, (November 14, 2011); S. Llyod-Roberts, *Have India’s poor become human guinea pigs?*, BBC NEWS, (November 1, 2012); European Center for Constitutional and Human Rights, Case Summary, *Human Rights violations in clinical trials in India, the case of the HPV vaccination project*, (February 11, 2014), available at www.ecchr.eu

⁸⁶ Department Related Parliamentary Standing Committee on Health and Family Welfare, Seventy-Second Report, *Alleged Irregularities in the Conduct of Studies using Human Papilloma Virus (HPV) Vaccine by Path in India*, (August 30th, 2013: Rajya Sabha) available at <http://164.100.47.5/newcommittee/reports/EnglishCommittees/Committee%20on%20Health%20and%20Family%20Welfare/72.pdf> (last accessed on June 2, 2018)

consent form (along with the thumb impressions of the participant or participant's guardian) as a witness to the consent process.⁸⁷ The report also mentions that the witnesses in such cases have to be full-time government employees and have to be responsible for explaining the information to the person. However, the report found that the signatures of such witnesses were missing.⁸⁸ If the Parliamentary Committee's report is read *in toto*, it reveals that not only was the competence of parties not properly ascertained, but there was also a lack of understanding of the information involved.

This case shows that in cases where participants lack capacity, there are problems with how their capacity or that of their legally authorised representatives is ascertained in practice. First, hostel wardens of schools do not qualify as legally authorised guardians for minors under the Indian Guardians and Wards Act, 1890. The same would apply to clinic wardens for hospitalised mentally incapacitated individuals. Second, the requirement of finding a full time government employee to witness a consent process and to explain the information to the illiterate or incapacitated person (or to the guardian of such persons) could be extremely cumbersome in practice. Although such a requirement was possibly introduced to ensure transparency and should be commended, it serves little purpose as far as ascertaining participant's capacity to *understand* is concerned. By such capacity I mean the ethical test for capacity, i.e., a person showing the ability to assess the risks and benefits of a study and showing an understanding of the consequences of one's decisions. Third, the HPV case raises a fundamental problem, that of having no

⁸⁷ *Supra* note 3.

⁸⁸ This was just one of the discrepancy recorded from the numerous, like one person seemed to have signed around seven forms, and "the warden/teachers/headmasters were not given written permission by the parents/ guardians to sign on behalf of their girls. (ii) On many forms witness had not signed and of the forms which are signed, it is not clear whether they are signed by full time government employees, as per rules.(iii) Neither the photograph nor the photo ID card of parents/guardians/wardens is pasted in consent form. (iv) On many forms investigator has not signed. (v) On some forms signature of parents/guardians is not matching with their names. (vi) The date of vaccination is much earlier than the date of signature of parents/guardian in the consent forms. Apparently they were obtained post-facto.(vii) In some forms, the name is of the father but the signature is probably of the mother (lady's name)." See ¶ 6.14, Parliamentary Committee Seventy Second Report (2013) *supra* note 86.

safeguards in place *during* the consent process. There is no independent (one who is not a government employee for a government-supported initiative) reviewer to oversee that the consent forms are being signed in due compliance with the three major ethical requirements. Fourth, an inquiry made after-the-fact that looks at consent forms to ascertain if the participants had capacity does not accurately reflect that the participant or the guardian, at the time of consenting, showed that she could reasonably assess the consequences of her decisions pertaining her herself or her guardian. This is because merely the signature on a consent form does not reflect either the mental capacity (pertaining to a clinical judgment on the soundness of mind) or the ethically understood requirement of capacity. Therefore, capacity assessment methods have been designed for such situations.

Numerous assessment methods have been developed to assess the competence of adults.⁸⁹ As Grisso and Appelbaum have noted, what counts as impaired decision-making capacity is partly determined by the standard of competence that is chosen to assess competency in adults.⁹⁰ It is largely agreed that a prospective research participant's capacity to decide whether to participate in a particular research project cannot be determined through a general mental status assessment.⁹¹ Therefore, the investigators ought to develop and present the specific information relevant to their study and evaluate the prospective participant's understanding and appreciation of that information. Such evaluation must also ascertain a participant's *continuing* ability to be able to understand the information throughout the course of the trial. The role of the researcher/investigator is key in

⁸⁹ T. Grisso & P. S. Appelbaum, *Comparison of Standards for Assessing Patients' Capacities to Make Treatment Decisions*, AMERICAN JOURNAL OF PSYCHIATRY, VOL. 152, (1995), pp. 1033–37. An overview of the different assessment tools developed for assessing competency in treatment and research contexts, including, but not limited to, the Hopkins Competency Assessment Test (HCAT), MacArthur Treatment Competence Study (MTCS), MacArthur Competence Assessment Tool—Treatment (MacCAT-T), The Mini Mental Status Examination (MMSE), etc., can be found in the following article. See E.D. Sturman, *The capacity to consent to treatment and research: A review of standardized assessment tools*, Clinical Psychology Review, Vol. 25, (2005), pp. 954 – 974.

⁹⁰ *Id.*

⁹¹ D. M. High, et al., *Guidelines for Addressing Ethical and Legal Issues in Alzheimer Disease Research: A Position Paper*, ALZHEIMER DISEASE AND ASSOCIATED DISORDERS, Vol. 8, Supp. 4, (1994), pp. 66–74; R. J. Bonnie, *Research with cognitively impaired subjects: Unfinished business in the regulation of human research*, ARCHIVES OF GENERAL PSYCHIATRY, Vol. 54, Issue No. 2, (February, 1997), pp. 105-11.

ascertaining the competence of the individual and ensuring the success of an informed consent procedure. However, from my interviews with investigators in India, the general attitude towards competence was the levelling of capacity with the legalistic requirement of age and soundness of mind. Although soundness of mind is almost always presumed in all cases, even if there was indication of unsoundness, there are no capacity assessment tests mentioned anywhere, neither in a statute (akin to MCA in the UK) nor in the ethical guidelines. Such attitude of levelling the capacity requirement with age does not prove competence as ethically understood.

The next section will bring to fore another aspect of capacity in action that has been given little attention in India.

6.3.2. What about therapeutic misconception?

My empirical research brought to the fore another factor that seems to affect the capacity of an individual to participate in clinical research, although there are hardly any studies from India evaluating the effects of it. Bearing in mind the differences outlined in Chapter 3 between medical treatment and clinical research, it becomes important to discuss the role of ‘therapeutic misconception’ while discussing capacity. Therapeutic misconception occurs when a research subject fails to grasp the distinction between the imperatives of clinical research and of ordinary treatment.⁹² Such a misconception of a clinical trial makes a participant inaccurately attribute notions of therapeutic intent and individualized care to trials, notions that are usually synonymous with treatment.⁹³ Studies have shown that despite adults possessing the necessary competence to make decisions about participating in research, therapeutic misconception about the trial impairs their ability to reason efficiently thereby inflicting doubts on competence.⁹⁴ Many studies have found that subjects frequently

⁹² G. E. Henderson, *Clinical Trials and Medical Care: Defining the Therapeutic Misconception*, PLoS Med, Vol. 4, Issue no. 11, November 2007.

⁹³ P. S. Appelbaum, et al., *The Therapeutic Misconception: Informed Consent in Psychiatric Research*, INTERNATIONAL JOURNAL OF LAW AND PSYCHIATRY, Vol. 5 (1982), pp. 319-329; P. S. Appelbaum, et al., *Therapeutic misconception and the appreciation of risks in clinical trials*, SOCIAL SCIENCE AND MEDICINE, Vol. 58, Issue no. 9, (2004), pp. 1689–1697.

⁹⁴ See C. W. Lidz, *The Therapeutic Misconception and Our Models of Competency and Informed Consent*, BEHAVIOURAL SCIENCES AND THE LAW, Vol. 24, (2006), pp. 535–546 (2006).

overestimate the likely benefits of entry into research studies.⁹⁵ Such a misconception leads them to underestimate risks,⁹⁶ confuses them about the nature of randomized assignment,⁹⁷ and generally leads participants to mix up research with ordinary treatment.⁹⁸ An investigator I interviewed told me about such problems while recruiting for trials but without quite using the expression ‘therapeutic misconception’. He said:

There are times people expect trials to give them a cure for everything, they expect too much. When they realise they are not benefitting medically, they either drop out or become difficult.

This perception of the investigator might raise the question - was the trial participant not adequately informed that trials have different objectives than medical treatment? Some empirical studies show that despite there being adequate disclosure some trial participants still hold on to such misconceptions.⁹⁹ This suggests that having the

⁹⁵ C. Daugherty, et al., *Perceptions of cancer patients and their physicians involved in phase I trials*, JOURNAL OF CLINICAL ONCOLOGY, Vol. 13, Issue No. 5, (1995), 1062-1072. In this study 27 out of 30 consecutive cancer patients who agreed to participate in a Phase-I oncology trial filled out a survey where 85% of patients said that they decided to participate the trial for reasons of possible therapeutic benefit. See also, J. D. Cheng, et al., *Impact of Quality of Life on Patient Expectations Regarding Phase I Clinical Trials*, JOURNAL OF CLINICAL ONCOLOGY, Vol. 18, Issue No. 2, (2000). This was a questionnaire-based study conducted on 30 cancer patients who enrolled in a Phase I clinical trial, and included their physicians. The study results showed that when compared with their physicians, the patients overestimated potential benefits and toxicities from experimental therapy (mean expected benefit, 59.8% v 23.8%, $P < .01$; mean expected toxicity, 29.8% v 16.0%, $P < .01$). The patients also estimated a greater potential for benefit (59.8% v 36.8%, $P < .01$) and less potential for toxicity (29.8% v 45.6%, $P = .01$) for experimental therapy as compared with the standard therapy.

⁹⁶ For instance, a study was conducted on 207 participants in trials that assessed a cancer-directed treatment (which does not include supportive care), these were phase I safety and dose-escalation trials, safety trials, phase II single-group efficacy trials, or phase III randomised controlled trials. Using the Quality of Informed Consent (QuIC) questionnaire the researchers found that about 63% of the trial subjects did not recognise the potential for incremental risks from participation, see S. Joffe, et al., *Quality of informed consent in cancer clinical trials: A cross-sectional survey*, LANCET, Vol. 358, (2001), pp. 1772–1777.

⁹⁷ K. Featherstone & J. L. Donovan, “*Why don’t they just tell me straight, why allocate it?*” *The struggle to make sense of participating in a randomised controlled trial*, SOCIAL SCIENCE AND MEDICINE, Vol. 55, (2002), pp. 709–719. In this study, 33 middle aged or older men, with lower urinary tract symptoms related to benign prostatic disease, were interviewed using semi-structured, in-depth interview format. The data analysis showed that most held contradictory views about their treatment allocation, leading the researchers to conclude that “most eligible patients, whatever their level of knowledge, will struggle to make sense of their participation in randomised trials.”

⁹⁸ Joffe, et al., (2001), *supra* note 96.

⁹⁹ G. E. Henderson, et al., *Therapeutic misconception in early phase gene transfer trials*, SOCIAL SCIENCE AND MEDICINE, Vol. 62, (January 2006), Issue No. 1, pp. 239-53. In this study, semi-

cognitive ability to make rational decisions and receiving adequate information does not necessarily lead to an adequate understanding of the issues at hand. Therefore, such issues can only be addressed through transparent communication between the researcher and the subjects and the clear mention of the likelihood of benefits being low or none at all.¹⁰⁰

If we are to assess competence using the four-element model given by Grisso and Appelbaum,¹⁰¹ the competence of individuals to make decisions regarding trial participation cannot be reduced to simply age or soundness of mind. Bureaucratic methods of assuring that consent forms are duly signed by guardians of incapacitated persons is also not sufficient evidence of capacity to consent. The onus of ethicality in making sure that consent is ‘understood’ and ‘informed’ by a ‘competent’ person lies upon the investigator of the trial (or recruiters for trials).

6.4. Conclusion

This chapter is the first part of the two-chapter discussion on the research findings accumulated through semi-structured interviews of various stakeholders involved in clinical research in India. But even if we assume that the criteria mentioned in Sections 5.1-5.3 have been met with, debates about informed consent do not rest there. The concept of autonomy has been used as the predominant justification for informed consent since the 1970s.¹⁰² But is it the only justification for informed

structured interviews were conducted on 68 subjects from early phase gene transfer trials. The researchers found that many subjects adopted investigators of the study as their doctors during the study, which led to higher levels therapeutic misconception. However, the study suggested that subjects could distinguish between the treatment and research without overestimation of benefits if the communication was more transparent and if the consent forms mentioned that the likelihood of benefit was low.

¹⁰⁰ *Id.*

¹⁰¹ As mentioned in Chapter 3, these were: i) the ability to communicate choices; ii) the ability to understand information about a treatment decision; iii) appreciating the situation and its consequences; iv) rational manipulation of information, meaning “the ability to use logical processes to compare the benefits and risks of various treatment options”. See, P. S. Appelbaum & T. Grisso, *Assessing Patients' Capacities to Consent to Treatment*, THE NEW ENGLAND JOURNAL OF MEDICINE, Vol. 318, (1988), pp. 1635-1638.

¹⁰² FADEN & BEAUCHAMP (1986), p. 8, *supra* note 1; The Belmont Report, (1979), Part B (1); BEAUCHAMP & CHILDRESS, (2009), Chapter 4. *See ALSO* G. DWORKIN, THE THEORY AND PRACTICE OF AUTONOMY, (Cambridge: Cambridge University Press, 1988); A. E. BUCHANAN & D. W. BROCK, DECIDING FOR OTHERS: THE ETHICS OF SURROGATE DECISION-MAKING, (Cambridge: Cambridge

consent? What do various stakeholders think about autonomy? The next chapter will consider the existing debates surrounding the justification for informed consent while keeping in mind the practitioner perspectives. It will also evaluate the perspectives of various stakeholders on the role of law and ethics in ensuring good ethical conduct in clinical research.

FINDINGS & ANALYSIS: JUSTIFICATIONS & ROLES

7.0. Introduction

This chapter continues to answer the empirical question: How is the principle of informed consent perceived by the different stakeholders involved in the process of informed consent in clinical research in India? The previous chapter focused on stakeholders' perspectives of what the essential features of informed consent entail and contrasted it with the theoretical understanding of the principle. This chapter will address two other themes that emerged from the semi-structured interviews. These are interviewees' views on autonomy and the role of law and ethics in ensuring ethical conduct in clinical research in India. These themes follow the same format as the previous chapter in presenting the views of stakeholders alongside the theoretical discussions pertaining to this area.

7.1. AUTONOMY AND OTHER JUSTIFICATIONS

Protecting participant autonomy is the predominant justification given for informed consent. According to bioethicists Beauchamp and Childress:

The autonomous individual acts freely in accordance with a self-chosen plan, analogous to the way an independent government manages its territories and establishes its policies.¹

However, the bioethicists stress that autonomy so understood differs from autonomy as acting on one's own will, a perspective that is often supported by other philosophers.² There is also the qualification that autonomy here differs from many

¹ T. L. BEAUCHAMP & J. F. CHILDRESS, *PRINCIPLES OF BIOMEDICAL ETHICS*, (New York: Oxford University Press, 2009, 6th edn), pp. 99-100.

² *Id*, p. 100-101. Here it is important to mention the distinction drawn by Savulescu and Stein between the libertarian and liberal conceptions of autonomy. They say that the "libertarian conception of autonomy rejects paternalistic interference—interference that purports to be for the person's own good—as well as interference motivated by other goals. The dominant liberal conception of autonomy also condemns force and fraud. But the liberal conception endorses a degree of paternalism that sets it apart from the libertarian conception." I am aware that readers reading this might belong to either the libertarian or the liberal camp. I have excluded long conceptual discussions on autonomy in this thesis and am not committed to any one account. I mention autonomy only to the extent of how it appears in my empirical research, and because I look at how the practice interacts with ethics and law, I have chosen the conceptualisations that best suit a given empirical viewpoint. Therefore, one might notice that I refer to both conceptions in my analysis. See M. S. Stein & J. Savulescu, *Welfare versus*

other uses of autonomy in bioethics and biolaw.³ Beauchamp and Childress also admit that actions can be autonomous by degrees. This means that an act can be less autonomous than another (perhaps due to varying degree of influences over decision-making ability), but such varying degree does not imply that the act was not autonomous. Considering the varying notions of individual autonomy, some scholars have challenged the autonomy-based justifications for informed consent.⁴ Scholars have also criticised the individualistic nature of autonomy for being identity-based with too much focus on the nature and character of the self. Olweny writes:

The concept of autonomy is a manifestation of Western culture, which emphasises individualism, personal happiness and self-actualisation. In this context, “personhood” is viewed from the perspective of autonomy and individual rights.⁵

If this is true, can a person with non-western religious ideals, traditional or community norms, where “self-chosen plans” are dependent on others, still be autonomous? This was rather the trail of thought of one of the officials from ICMR, who I interviewed regarding the mention of informed consent in the ICMR Ethical Guidelines related to Human-Subject Research in India.⁶ The official said:

India is complicated and huge...its cultures and values vary from place to place. You [pointing at the researcher] look at your own background and answer if most people in India have the kind of autonomy that people in the Western countries have. If we conduct research with a female participant in a rural or semi-urban area...the participant's mother-in-law, the *panchayat* head [head of the village], along with many others would also have to give

Autonomy in Human Subjects Research, FLORIDA STATE UNIVERSITY LAW REVIEW, Vol. 38, Issue No. 2, (2011).

³ G. DWORKIN, *THE THEORY AND PRACTICE OF AUTONOMY*, (Cambridge: Cambridge University Press, 1988), p. 101.

⁴ N. C. MANSON & O. O'NEILL, *RETHINKING INFORMED CONSENT IN BIOETHICS*, (Cambridge University Press, 2007), p. 212; *See also* O. O'NEILL, *AUTONOMY AND TRUST IN BIOETHICS* (Gifford Lectures at the University of Edinburgh), (Cambridge University Press, 2002), in which O'Neill argues against using protection of individual autonomy as a justification for informed consent. She states that since the feasibility and the value of all conceptions of individual autonomy are hotly contested, the justification for informed consent cannot be merely based on securing individual autonomy.

⁵ C. Olweny, *The ethics and conduct of cross-cultural research in developing countries*, *PSYCHO-ONCOLOGY*, Vol. 3, Issue No. 1, (1994), pp. 11-20.

⁶ Indian Council of Medical Research (ICMR), *Ethical Guidelines on Biomedical Research on Human Participants*, October 2006, p. 1, available at http://www.icmr.nic.in/ethical_guidelines.pdf

permission to the female to participate in a scientific research of that manner. So local values always differ...that is why ICMR mentioned in the Guidelines that one has to consider autonomy versus harmony of the environment of the trial participants.

Such concerns led the Council for International Organizations of Medical Sciences (CIOMS) to amend the international guidelines to include the guideline that trial investigators and sponsors should carry out informed consent procedures in “culturally appropriate” ways.⁷ Beauchamp and Childress have admitted that a person can autonomously choose to be guided by religious, traditional, or community norms and values. Although they concede that it can sometimes be difficult to take into account diverse values and beliefs while sharing the information necessary for decision-making, it is still no excuse for not allowing autonomous decision-making. They write, “autonomous choice is a *right*, not a *duty* of patients”.⁸

When Beauchamp and Childress gave their conceptualisation of autonomy as applicable to bioethics, they aimed to construct:

[A] conception of respect for autonomy that is not excessively individualistic (neglecting the social nature of individuals and the impact of individual choices and actions on others), not excessively focused on reason (neglecting the emotions), and not unduly legalistic (highlighting legal rights and downplaying social practices).⁹

However, critics of rationalistic and individualist ideals of autonomy hold that despite such efforts on Beauchamp and Childress’ part, their traditional notion of autonomy has not paid attention to the individual relationships and social dimensions of autonomy. This has given impetus to the development of the concept of relational autonomy. The relational autonomists argue that their version of autonomy gives the most helpful account of decision-making in medicine. Relational autonomy holds that:

⁷ Guideline 9, on Consent, International Ethical Guidelines for Health Related Research Involving Humans, Council for International Organizations of Medical Sciences (CIOMS), p. 35, available at <http://cioms.ch/ethical-guidelines-2016/WEB-CIOMS-EthicalGuidelines.pdf>

⁸ BEAUCHAMP & CHILDRESS (2009), p. 105-106, *supra* note 1.

⁹ T. L. BEAUCHAMP & J. F. CHILDRESS, PRINCIPLE OF BIOMEDICAL ETHICS, (Oxford University Press, 5th edn., 2001), p. 57.

[T]here is a social component built into the very meaning of autonomy, [autonomy] involves a dynamic balance among interdependent people tied to overlapping projects...[The autonomous self is one] continually remaking itself in response to relationships that are seldom static,[and which] exists *fundamentally* in relation to others.¹⁰

Autonomy as a concept, as evident, is hugely contested in ethics. But in practice, how much are the recruiters for trials looking to protect the autonomy, as understood by them, of the trial participant? This question can partly be answered through the kind of informed consent procedures followed by the recruiters and their own categorisation of such procedures. A representative of a pharmaceutical company told me that for her it was “interesting to see how socio-economic conditions influenced people’s decisions” but she said that for practical matters “informed consent procedures are quite standard”. The company representative said that they had manuals for investigators to teach them how consent had to be taken from “different groups of people”, and they “never had any problems with consent”. However, extreme standardisation of procedures can lead to procedures becoming barely more than tick-box exercises. By ‘tick-box exercise’, I mean the consent procedure does not prove that the consent was *informed*; rather it only proves that there was *signed* consent.¹¹ But when I asked the researcher about what he understood by autonomy of a participant, he said:

...that the decision is their own. I know it is this, but this rarely happens because decisions are always influenced and family permissions have to be taken, and all those things...Our priority is to keep our participants safe, that is what matters in the end.

Aiming for participant safety is fine, but to do so it is ethically required of a researcher to ensure that a participant’s act of consenting to a study is an autonomous act, i.e., an act in accordance with her “self-chosen plan”. Considering the socio-

¹⁰ A. Donchin, *Autonomy and Interdependence: Quandaries in Genetic Decision Making*, In: C. MACKENZIE & N. STOLJAR (EDS.), *RELATIONAL AUTONOMY: FEMINIST PERSPECTIVES ON AUTONOMY, AGENCY, AND THE SOCIAL SELF*, (Oxford: Oxford University Press, 2000), pp. 236-258, at p. 239.

¹¹ This can also be bracketed as the procedure which only shows that participants had the *capacity to act* autonomously, but whether or not the *act* was autonomous would be a different question altogether. Faden and Beauchamp give numerous illustrations of cases where they differentiate between autonomous acts and autonomous individuals in: Chapter 7, *Concept of Autonomy*, in: R. R. FADEN & T. L. BEAUCHAMP, *A HISTORY AND THEORY OF INFORMED CONSENT*, (NEW YORK: OXFORD UNIVERSITY PRESS: 1986).

economic conditions in India, this brings me to discuss another general, and perhaps reasonable, assumption that poverty limits choices. But this assumption often leads to the conclusion that a poor person being offered money or incentives to participate in research did not make an autonomous choice for lack of availability of meaningful choices. One is intuitively aware that a poor person with no access to health care has a limited set of choices. Here is another set of plausible assumptions:

(1) that a person's ability to exercise her autonomy in the pursuit of her values would be enhanced by the introduction into her choice-set of additional options that she would value, and (2) that if new options are introduced into a person's choice set that she does not value this would not adversely affect her ability to exercise her autonomy.¹²

Given these reasonable assumptions, it can be argued that any person who values “the ability of persons to exercise their autonomy in the pursuit of their values”¹³ or according to their “self-chosen plan” should approve the introduction of a new option into their choice-sets. Here it would mean that the new option would be participation in trial for some form of incentive which was not an option before. Now a person still has the freedom to choose between *status quo* and the new option. Many scholars argue that, in situations where there are limited choice-sets available, autonomy is enhanced through the introduction of new options.¹⁴ This was perhaps what one investigator meant when he said:

¹² C. Freiman, *Vote Markets*, AUSTRALASIAN JOURNAL OF PHILOSOPHY, Vol. 92, Issue No. 4 (2014), 759-774. Freiman's assumptions, although given for allowing vote selling, would find support from Gerald Dworkin, Taylor, and Savulescu, who have supported a market in organ trade for the similar reason that introducing new options enhances autonomy of a person, See G. Dworkin, *Market and Morals: The Case for Organ Sales*, in: G. DWORKIN, MARKET AND MORALS, (Westview, 1994); J. S. Taylor, *Autonomy, Constraining Options, and Organ Sales*, JOURNAL OF APPLIED PHILOSOPHY, Vol. 19, No. 3 (2002), pp. 273-285; Savulescu writes, “Poverty which is acceptable to a society should not be a circumstance which prevents a person taking on a risk or harm to escape that poverty. It is double injustice to say to a poor person: “You can't have what most other people have and we are not going to let you do what you want to have those things”. When people go to war voluntarily, risking their lives for their country, they are heralded as heroes. If we allow people to die for their country, it seems to me we should allow them to risk death or injury for the chance to improve the quality of their lives or their children's lives or for anything else they value. Money for these people is just a means to realise what they value in life.” See J. Savulescu, *Is the sale of body parts wrong?*, JOURNAL OF MEDICAL ETHICS, Vol. 28, Issue No. 3, (2003).

¹³ *Id.* Freiman (2014)

¹⁴ *Supra* note 12.

Our job should not be to judge why or how people are making decisions...we advertise. Interested people come to us. We explain the best way we can, the risks and benefits and everything and then we leave it to them to make the decision. Should we sit and counsel people on what we think is the best option for them? I am sure no ethics says [sic] that. If someone participates for the money, or for the drug, or for the [medical] check-up, it is his choice. It is bonus if he gets something he needed...we should be clear that they are never forced to make a choice.

Many might still see *some* moral wrong in the scenario. Perhaps concerns of exploitation arise (which fall outside the scope of the thesis), but some would call such cases mutually advantageous cases of exploitation, hence, permissible.¹⁵ Whether there is a moral wrong in conducting for-profit trials in developing countries with large disadvantaged populations is far from a settled ethical debate. But both the concepts of autonomy and exploitation are heavily debated theoretical concepts that have not yet found a *clear* expression in law.¹⁶ The legal silence on

¹⁵ The fact that India has not been able to provide *adequate* health care to a large percentage of its population still begs the empirical question: how many of the people deprived of quality health care do actually participate in a trial, when fully informed of the risks and benefits, only to get access to health care? Furthermore, even if some do participate in a trial for the sole motive of getting access to health care, having been informed of the implications of such participation, should their voluntary consent be considered invalid? Some authors have addressed such questions in detail. For instance, according to Emanuel, if “(1) the consent condition is satisfied (B is not coerced by A); (2) there is mutual benefit (B is not harmed by A); (3) B receives a fair share of benefits, where fairness is determined according to whether B’s own preferences regarding the content and scope of her share are satisfied”, then clinical trials in developing countries would qualify as “mutually advantageous exploitative transactions”. However, he opines that such transactions would not be normatively problematic (i.e., would not warrant prevention) as long as the above stated conditions are satisfied. See E. J. Emanuel, *Addressing exploitation: Reasonable availability versus fair benefits*, see also Wertheimer’s Principle of Permissible Exploitation (PPE), A. Wertheimer, *Exploitation in Clinical Research*, both as chapters in: J. S. HAWKINS & E. J. EMANUEL (EDS) *EXPLOITATION AND DEVELOPING COUNTRIES: THE ETHICS OF CLINICAL RESEARCH* (Princeton University Press, 2008), at pp. 298-303 & at pp. 73-74 respectively.

¹⁶ By this, I mean that the concepts per se have not been defined under (institutionalised) substantive law, although many legal rights *derive* from the concepts. A violation of autonomy per se is not a legal wrong. In fact, the legal paradox is that if autonomy is understood as *freedom to choose* then it can be argued that all proactive law enforcement tends to violate the autonomy of those subject to it. As for exploitation, jurisdictions usually pass laws against instances of specific exploitative practices; in such cases, the content of what would be termed exploitation is specifically outlined as opposed to simply saying, “This is unfair, hence, illegal”. (For instance, in the US, the State of North Carolina makes exploitation of an elder adult or disabled adult a specific offence, but such exploitation is only when someone cheats the adults out of their property, see § 14-112.2 of North Carolina General Statutes). For instances of exploitative transactions, which could be consensual and beneficial to both parties involved (and that are relevant to this discussion), the authority to make such transactions

these concepts as well as the views of researchers on these issues indicates these issues are not real concerns for legislature and researchers alike.

Departing from autonomy-based justification of informed consent, some philosophers claim “informed consent... is generally important [to some extent] because it can make a distinctive contribution to the restoration of trust.”¹⁷ Some see informed consent as a fundamentally valuable way to honour the trust that the patient places in the physician, and as part of the fiduciary role that the physician has undertaken.¹⁸ By corollary, this would mean that it serves as a way to honour the trust the participants place on the trial investigators. In practice, the concept of shared decision-making due to trust often comes up when decisions depend on the participant’s trust in her doctor, as one investigator, who is also a doctor at a public hospital, told me:

Sometimes there are patients who like to be told what is good for them...these are trickier cases for informed consent because there is the attitude that the doctor knows better and in most cases it is actually true...sometimes there are molecules in compounds of some medicines that are being tested so we cannot tell them if that one is going to suit a particular person or not...we mainly recruit participants with a particular health condition and prerequisites...there are always some risks we do not know about. Some patients ask “what do you think, should I do it?”...what does one say there? If you're sure there is not much of a risk then we advise them...why not....most times when they ask us and we think there might be a risk we tell them to make the decision themselves.

Such situations, including situations where a person wholly delegates the task of decision-making to her physician, can also be covered under Gerald Dworkin’s idea of critical reflection on autonomy.¹⁹ Under this version of autonomy, there is room for a person’s conscious submission to some form of external authority (for example, a physician, a religion, a leader, and so on). Situations such as those described by the investigator above can be covered under this theory because it has room for a

illegal depends upon the will of legislatures. For this thesis, I do not commit myself to any particular theory of exploitation or autonomy.

¹⁷ O. O’NEILL, (2002), p. 145, *supra* note 4.

¹⁸ S. Joffe & R. D. Truog, *Consent to medical care: the importance of fiduciary context*, In: F. G. MILLER & A. WERTHEIMER (EDS.), *THE ETHICS OF CONSENT*, (New York: Oxford University Press, 2010), p. 352.

¹⁹ G. DWORKIN, (1988), *supra* note 3.

physician to play a paternalistic role. The central idea behind this account of autonomy is critical reflection on decisions, which means that after critical reflection on their preferences, patients may choose to let the physician decide which treatment is best. This also applies to cases where participants ask their physicians if they should or should not volunteer for a trial. This shows that there are accounts of autonomy that could partly include other justifications for informed consent, like honouring the trust placed in the physician/investigator. This could also be interpreted as a situation wherein a trial participant waives the right to informed consent, as many participants would rather have physicians make certain decisions for them. Beauchamp and Childress have noted that informed consent is a patient's right, not her duty. This if taken further implies that as informed consent serves autonomy, it ought to be autonomously waivable.²⁰

With every different conceptualisation of autonomy, there will be someone who will argue against it. Such is the nature of the ethics. Therefore, one might prefer another, and perhaps simpler, justification for informed consent, which is the protection of the trial participant from abusive conduct.²¹ An unequal power relationship (asymmetrical relationship) exists between an investigator and a trial participant. Investigators are better informed than participants about both the procedures involved and potential results that may follow from the trial. The procedures and results of the trial are often unknown or of no medical benefit to participants, which may create a disincentive to participate. To recruit volunteers for trials, investigators might be tempted to resort to options that involve assault, deceit, coercion, and exploitation.²² Informed consent reduces the scope of employing these options for clinicians and investigators. For instance, by placing the duty upon the investigators to disclose information about the trial, informed consent minimises the information gap between clinicians and participants, thereby making the latter group less vulnerable to certain abuses of conduct. Of course, informed consent by itself does not protect participants from *all* abuses of conduct. That, however, hardly

²⁰ BEAUCHAMP & CHILDRESS, (2001), p. 106, *supra* note 9.

²¹ N. Eyal, *Informed Consent*, *THE STANFORD ENCYCLOPAEDIA OF PHILOSOPHY*, (Fall 2012 Edition), available at <https://plato.stanford.edu/archives/fall2012/entries/informed-consent/> (last accessed on June 2, 2018)

²² MANSON & O'NEILL (2007), p. 75, *supra* note 4.

undermines the fact that informed consent protects participants from significant forms of abusive conduct. An advantage of this justification is that it makes it easier to argue for stronger laws regulating informed consent procedures. A proposition demanding stronger laws would require evidence that the abuses of conduct by the investigators deserve measures to be minimised and that only by strengthening informed consent measures would such abuses of conduct be minimised. This raises the question - do we need stronger laws for implementing informed consent or do ethical guidelines suffice in minimising abusive conduct of investigators and trial recruiters? The next section will consider this important question from the perspective of various stakeholders.

7.2. ROLE OF LAW AND ETHICS

An important theme that stood out in my interviewee data was their views on stricter laws and the ethics of clinical research. Chapter 4 of this thesis elaborated upon the legal position of informed consent in India. It was noted that for dealing with lack or inadequacy of informed consent in clinical research some legal redress is available. For instance, under tort law, under the Indian Penal Code, 1860, (criminal law) for more serious cases of physical injury without consent, and under the Indian Constitution for violation of the fundamental right to life under Article 21. However, there are no penal provisions under the Drugs and Cosmetics Act, 1940, for failure to take informed consent as laid out under Schedule Y. Moreover, under the Code of Ethics Regulation, 2002, if an investigator is a registered doctor, the punishment comes in the form of removal of their name from the register of practitioners either for a limited period or permanently. The chapter also discussed that the right of private action for research subjects/trial participants is not as well-defined as it is in the context of negligent medical treatment under common law. This legal situation has led to a demand by the civil society for stricter laws for protecting trial participants in India, which, inferentially, is a demand for sanctions aimed at the investigators/recruiters of trials for the breach of informed consent requirements.

But how much would stricter laws lead to ethical conduct in clinical research? Most of the stakeholders I interviewed expressed some sort of ambivalence about legal solutions to ethical conundrums in clinical research. For most of them,

strict penalties were *necessary* for gross violation of rules related to informed consent but laws were not *sufficient* for bringing about ethical conduct. I interviewed an investigator based at a public hospital in Mumbai, who said:

If you are asking that if more laws are needed to make research more ethical then I would say maybe not, because we all know what our duties are and there are enough guidelines telling us what to do. Sometimes there are laws but people still do what is wrong especially when they know there are little chances of them getting caught and if they see it is easy to get away...of course there needs to be something to punish total criminals...Maybe what we need is better regulation so there is pressure of being constantly monitored. That would help. Penalties, jail time...do these things really help...will that make trials more ethical? I don't know.

It is noteworthy that this investigator thought that better regulation to monitor trials would be more suitable for ensuring ethical conduct than stricter laws. This investigator's ambivalence about the force of law in assuring stricter compliance with the standards of informed consent was shared by an ICMR official. On being asked about the problem of poor and inadequate informed consent procedures in research in India, the official identified "lack of penal provisions in the Drugs and Cosmetics Act, 1940, not only for the lack of informed consent, but also for flaws or shortcomings in the overall research design". But when asked if the official saw stricter penalties as a solution to problematic ethical issues in human subject research, the official answered that in official capacity the answer would be a "yes, definitely", but "in personal capacity, it would be a no". Such duality in position makes sense because I was informed that the ICMR is pushing for a law that appoints a central bioethical authority in India for dealing with ethical violations in clinical research; such an authority would also be equipped with the necessary penalising powers. But for this official, the real problem was not lack of stricter penalties; it was the lack of research ethics training across the majority of medical and pharmaceutical colleges in the country. "If they are not aware of it, how will they implement it?" said the official, stressing the need to have more training programmes in bioethics and making research ethics a compulsory part of curricula across the nation. Another investigator from New Delhi reiterated similar worries as that of the ICMR official and said:

There is little thought given to ethics in research. It was not a compulsory course in my time [at medical college]. Now these things are being taken more seriously. ICMR officials and other people are teaching ethics at medical and pharmaceutical colleges. These will be the researchers of tomorrow and they need to know that it is unethical not to ask for consent before using someone else's body tissues, etc....My worry is that when the money starts coming in, a lot of people lose their sense of ethics.

The concern of this investigator about researchers having to worry about numerous other things than just ethics was evident in the manner in which all the investigators spoke about how difficult it was to conduct research in India. Almost all the investigators I interviewed spoke about the immense pressure that they had to work under. They spoke about tight deadlines, balancing jobs at hospitals/clinics and research, the pressure to create an international profile with good research publications, the administrative work related to funding of the study, the management of research staff, the re-training of clinicians according to sponsor standards, the sluggish bureaucracy, and so on. One investigator even suggested that I write about the struggles of being a research investigator in India rather than on informed consent. This is perhaps one of the reasons why stricter laws would not necessarily lead to ethical conduct. Remedial law has an obsession with fixing professional liability; this would not help address the heart of the problem which perhaps lies in the motivations and ability of investigators to follow ethical norms.

While writing about the limits of law in realising effective informed consent, Beauchamp opined that formulating legal standards, like those for information disclosure (as discussed in the previous chapter) would not help with ensuring good informed consent procedures in medicine or research. He writes:

Because courts are captivated by the context of after-the-fact resolution of narrow and concrete questions of duty, responsibility, blame, injury, and damages in specific cases, the law has no systematic way of affecting contemporary [bio]medical practice other than by a somewhat muted threat of prosecution for legal wrongdoing.²³

²³ T. L. BEAUCHAMP, *STANDING ON PRINCIPLES* (Collected Essays), (Oxford University Press, 2010), p. 68.

For Beauchamp, the heart of informed consent is moral and not legal. He writes that informed consent has more to do with understanding autonomous choice of research subjects than with the liability of professionals.²⁴ I mentioned in the earlier chapters that law had made an uneasy compromise with the ethical theory of informed consent, sometimes even making similar remarks as that of Beauchamp regarding the limits of law. The perceptions of the stakeholders seem to correlate to Beauchamp's view.

I asked a public health activist about what a stricter law would bring to the table that the current framework did not already have, after a long pause, he said:

Law complicates more than solves. People like going to courts because if they win, it is for everyone to see, it serves as a token victory. Law can change, but attitudes take longer to change.

If our goal is a change of attitude towards ethical procedures, then perhaps more laws are not the answer. This is also because India has a history of creating laws with poor implementation.²⁵ A bioethicist based out of New Delhi raised the problem of poor enforcement of laws in India, saying:

We will have more laws with poor enforcement. That is the situation in India. The new regulations will only be enforced till the dust over the controversies settle, and then it will be the same thing again.

These excerpts from the interviews regarding the role of law in ensuring ethical conduct share commonalities. The common theme among them all was that stronger laws will not necessarily lead to ethical conduct, and even if there are stronger laws, the enforcement of those will be poor. But here I would like to bring the attention of the reader to the previous chapters where we discussed *trust* as a justification of informed consent. If the rationale of informed consent is taken to be trust, then one could argue that stricter sanctions are likely to create an untrustworthy litigious

²⁴ *Id.*

²⁵ See generally S. K. DAS, INDIA'S RIGHTS REVOLUTION: HAS IT WORKED FOR THE POOR?, (Oxford University Press Canada, 2013). In this book the author looks at four Acts in particular, Right to Information Act, 2005; National Rural Employment Guarantee Act, 2005; Forest Rights Act, 2006; and The Right to Education Act, 2009. His in-depth analysis finds that "the laws, participatory framework, institutionalization, economic environment, and remedies mechanism have not been adequate to fulfil these rights for the poor.", at p. 304.

atmosphere between the trial participant and the investigator. If the trust based rationale is accepted, it is unclear if stricter sanctions would then help or defeat the purpose of informed consent.

As was noted at the beginning of this section, there are remedies available for breach of informed consent procedures leading to harm or serious injury. But there seems to be no blueprint on what stricter laws pertaining to informed consent are going to look like. If it means expansion of law to cover new ground, then that needs to be considered very carefully. There seems to be no legitimate purpose for having *stricter* laws that heavily penalise the mere breach of the one or the other condition of informed consent (without any resulting harm). Although there is still a need for clearer and firmer laws regarding lack of informed consent in research that cause injury or harm to the research participant.

Another important aspect that came to light regarding the attitude towards ethical norms was the *form* that such norms have taken. This was evident in the views of some of the stakeholders who seemed to think that the consent form and its content was decisive to prove compliance with the informed consent requirement. The next section looks at this in more detail.

7.2.1. Bureaucratised ‘form’ of Ethics

My interviews with different stakeholders revealed that the ethical guidelines have been formalised to resemble a tick-box exercise. The (over)emphasis on the requirement of the patient information sheet and *written* informed consent form, both under Schedule Y and under the ICMR ethical guidelines, have led to the equiparation of informed consent with the informed consent form. This critique of the formalisation of ethics, along with the Supreme Court orders in the *SAM case*, led the Ministry of Health and Family Welfare (MOHFW) in India to release a regulation requiring mandatory audio-video recording of the informed consent process for all trial participants. This regulation was later amended and audio-video recording of informed consent process was limited to cases where the participants

were vulnerable subjects.²⁶ There is, however, no clear definition of who falls under the category of a ‘vulnerable subject’, as has been discussed in Chapter 1. The following sections will explore different stakeholder views regarding the informed consent form and the lack of oversight mechanisms that threaten the goodwill behind the new regulations pertaining to informed consent.

A) The Consent Form

An empirical study conducted in India showed that trial participants perceived that signing the consent form meant waiving their right to claim damages and that consent gave more protection to the doctor/investigator and to the hospital than to the participant.²⁷ When I asked trial participants (A & B, from the previous chapter) if they had received copies of the consent form, they both said that they had not. One trial participant said that it was not much of a problem as signing the form was merely a “formality”. When the trial participants themselves view the process of informed consent, which is reduced to signing forms, as a mere formality, the principle of informed consent appears to have lost some of its value in action.

The status of the informed consent form has also been the subject of academic scrutiny. Scholars, in other jurisdictions, have written about the ambiguous nature of the legal status of informed consent forms.²⁸ Other scholars perceive the requirements for written signatures on consent forms as “legalistic rendering of the

²⁶ The Gazette of India, Ministry of Health and Family Welfare (MOHFW), Notification G.S.R. 611 (E), available at <http://www.ferci.org/wp-content/uploads/2014/07/Gazette-Notification-31-July-2015-AV-consent.pdf> (last accessed on June 2, 2018). The MoHFW released the blanket regulation to comply with the Supreme Court order dated 21.10.2013 asking the regulatory authorities to make audio-video recording of informed consent necessary for five Global Clinical Trials (GCTs) that were approved and supposed to be held after the *SAM case* was admitted in the Court. See DCGI notification dated 19.11.2013, available at <http://www.cdscsco.nic.in/writereaddata/Office%20Order%20dated%2019.11.2013.pdf> (last accessed on June 2, 2018).

²⁷ M. Vaz, et al, Listening to the voices of the general public in India on biomedical research - An exploratory study, *INDIAN JOURNAL OF MEDICAL ETHICS*, Vol. 12, (2015), pp. 68-77.

²⁸ G. Laurie & E. Postan, *Rhetoric or reality: What is the legal status of the consent form in health-related research?*, *MEDICAL LAW REVIEW*, Vol. 21, (2013), pp 371-414.

consent as a signed contract rather than a social process.”²⁹ An ICMR official also seemed confused about the exact purpose of the consent form, and said:

I have always wondered who does the informed consent form protect (pause) legally. Does it protect the investigator...the sponsor...or the patient?

While discussing the ethical requirement of capacity in the previous chapter, we saw how consent forms are evaluated after-the-fact when enquiries are made, which leads me to believe that the form’s status in India is limited to being an evidential proof of signed (or thumb impressed) consent to the requirements mentioned on the document. The problem that was raised in that section was that there are no independent overseers to observe whether the consent form is being signed in the context of the ethical requirements. Even if the by-laws require a full-time government officer or another independent person to attest as witness in cases of illiterate participants and minors, the important questions regarding all three requirements still remain open.

The formalisation of ethical requirements appears to lead to bureaucratisation (where paperwork is more important than the actual process) which in turn makes the consent process highly impersonal. Existing research has shown that many informed consent procedures become formalised decisions that leave little room for questions and dialogue.³⁰ Going back to the notion of relational autonomy as mentioned in section 6.1. above, the formalisation of informed consent procedures do not facilitate the building of relationships that create the room for reflection that is crucial for obtaining informed consent. An example of this is given by Spruit, et al, who write:

In a relationship in which there is strong dependency because of informational asymmetry, risk-bearers have less capacity to genuinely reflect on their options. Strong personal bonds, on the other hand, may enhance reflection as is revealed in the deliberative model of the doctor–patient relationship.³¹

²⁹ P. A. Marshall, *Ethical challenges in study design and informed consent for health research in resource-poor settings*, SOCIAL, ECONOMIC AND BEHAVIOURAL RESEARCH, Special Issue No. 5, (WHO, 2007), p. 32.

³⁰ S. Clarke S, *Informed consent without bureaucracy*, JOURNAL OF CLINICAL NEUROSCIENCE, Vol. 10, (2003), pp. 35–36.

³¹ S. L. Spruit, et al., *Informed Consent in Asymmetrical Relationships: an Investigation into Relational Factors that Influence Room for Reflection*, NANOETHICS, Vol. 10, (2016), pp. 123-138.

The research into analysing how relationships interact and leave open room for reflection is still in its nascent stage.³² But if this research is developed further, and considering that it seems to complement the concept of relational autonomy, it could help in ascertaining how genuine informed consent could be obtained from trial participants.

Regarding the new regulation of audio-video (AV) recording of consent procedure for vulnerable participants, it could, in principle, be helpful. However, the main issue with such recordings is: who will vet such recordings? Will it also be brought up as after-the-fact evidence to prove that the formality of recorded consent was complied with? Or will it actually make investigators more diligent in complying with the ethical standards? The latter is a question for further empirical research.³³ Audio-video recording of the consent process opens up questions about issues of confidentiality and privacy, which have, to a large extent, been addressed by the CDSCO under the draft guidelines released for conducting such recordings.³⁴ But doubts have been raised over its effectiveness in getting rid of the formalisation that plagued the informed consent form requirement. While commenting on the new

³² *Id.*

³³ During the write up phase for this PhD project a number of Indian scholars published papers in 2018 related to the working of the AV recording requirement for recording consent in India. In one paper the authors, who are also clinical research investigators, shared their experiences as well as those of other investigators and members of IEC monitoring committees, regarding the new AVR requirement for informed consent procedures. They outlined multiple challenges that they were facing pertaining to the new requirement. These were operational (poor sound and visual quality, improper visibility of investigator and participant); lack of proper infrastructure (some facilities do not have separate rooms for conducting recordings of consent procedure); the duration of consent procedures (the standard is 45 minutes; but recording duration should not be equalised with sufficiency of consent); testing of participants understanding (stressful for the investigator taking consent often at the cost of assessment of understanding of information by the participant); training of personnel involved in the study (frequently the investigators themselves do not take consent; instead the task is delegated to other team members who are often not adequately trained); the storage of data (the storage, archival and retrieval of recorded data must be proper to ensure confidentiality, therefore, researchers need to be trained). See P. A. Shetty, et al., *Audiovisual recording of the consenting process in clinical research: Experiences from a tertiary referral center*, PERSPECTIVES IN CLINICAL RESEARCH, Vol. 9, Issue No. 1, (2018), pp. 44-47.

³⁴ Central Drugs Standard Control Organisation (CDSCO), *Draft Guidelines on Audio-Visual Recording of Informed Consent Process In Clinical Trial*, (January 16, 2014), ¶ 3, available at http://www.cdsc0.nic.in/writereaddata/Guidance_for_AV%20Recording_09.January.14.pdf (last accessed on June 2, 2018).

regulations regarding clinical trials in India, a representative of a multinational pharmaceutical company said:

Nowhere else in the world is it compulsory to record consent in an audio-visual manner. Nowhere else in the world is there a formulae for compensating victims. These rules are unprecedented. But recording does not necessarily guarantee informed consent on the part of the participant; it may only reflect compliance with a formal process.

Similar ambiguity regarding the new regulations was expressed by an investigator in Mumbai who said:

Recording of informed consent procedures only adds to procedural burden in getting regulatory and ethics approval and it solves nothing.

While some find the new regulations cumbersome, a recent study on perceptions of investigators and trial participants on AV recording of consent revealed that some investigators found the new requirement helpful for documentation purposes.³⁵ However, the same study also revealed that some participants were uncomfortable with the recording of consent, and it was adversely affecting trial recruitment. Moreover, most investigators found the requirement “time-consuming” as they were required to take two consents (one for the trial, another for AV recording) and it took time away from patient care. Some investigators challenged the need for such a requirement with little to no guidelines given to them, while others endorsed it and thought they had to comply with it because it had legal implications.³⁶ Perhaps these studies are too early into the process and more guidelines might soon be released to tackle the current challenges in AV recording of consent. As one member of the CDSCO said:

We are looking into all the areas. New guidelines will soon be released for public comments and people can write to us about whatever issues they have with this requirement.

³⁵ This study was conducted in outpatient department-based anti-cancer drug trials and used a qualitative interpretative approach to semi-structured interviews, *see* B. Ganguly, *Newer Practice of Informed Consent Process of Clinical Trials in India*, ASIAN BIOETHICS REVIEW, Vol. 8, Issue No. 4, (2016), pp. 327-336.

³⁶ *Id.*

However, it is beyond doubt that the new requirement for recorded consent has increased the cost and procedural burden for the researchers. But if the protection of vulnerable participants is the goal, and if this is the way to do it, regulatory oversight will need to be much more efficient than it has been so far.

If we are to use protection and promotion of autonomy as the rationale for informed consent, a seemingly bureaucratic ritual like signing a consent form or recording a consent process does little to protect a person's expression of autonomy. Such rituals might be able to prove that the participant was autonomous in capacity (has reached the age of majority and is not of unsound mind, therefore, can make decisions), but the question remains open whether the *act* of consent was autonomous (consent to the trial in accordance with one's own will and "self-chosen plan").

Let us assume that, in the near future, signed paper consent forms will not be necessary at all, perhaps because the procedure has been replaced with audio-video recorded consent for *all* trial participants, or some other mechanism is put into place to register consent. Whatever the process, we would still need robust oversight mechanisms in place to ensure that the recorded consent tapes, disks, etc., are not tampered with, or that the participants are not giving consent to be recorded under undue influence, or that whatever loophole that exists in the process is being addressed by independent overseers. The following section will reveal the current state of affairs regarding lack of oversight mechanisms for informed consent procedures in India.

B) Lack of oversight mechanisms

Ethics committees are entrusted with the enormous task of protecting the trial participants and keeping research ethical. Some investigators/doctors interviewed for this research had also been members of Institutional Ethics Committees (IECs) for trials conducted at their hospitals. They were quite forthright in stating that their job as members of IECs was not to vet consent forms or recordings of consent procedures. The ethics committees' approval process appears before a proposed study goes into trial; hence, they are a pre informed consent *formality*. The role of the

ethics committee is to ascertain that the participants will be protected and that the study design has provisions to that effect. The role of IEC, among others, includes ascertainment of adequate informed consent procedures, like translation of consent forms in vernaculars, proper information leaflets about the study being handed out to the participants, etc. Although IECs have to review continuing reports from trial studies to check if there are any protocol deviations and monitor serious and adverse events (SAEs) arising during the course of the trial,³⁷ they do not conduct on-site monitoring. This is arguably an obstacle to ascertaining the thoroughness of the informed consent procedures. As one IEC member mentioned:

Ethics committees need to be given more teeth. There is a *sab chalta hai* [we are okay with everything] attitude as you might know...It works for most things here but should not work for ethical evaluation of studies. People who are knowledgeable and who know how to do ethical evaluations must man these committees...there is no point otherwise.

A health activist, an academic and a doctor by training, told me that he had been “randomly” asked numerous times to turn up for ethical evaluations “at the last minute” to simply even up the quota required for ethical approval. He said:

Such practices make you wonder how has clinical research happened in this country before 2014 or [20]15!...maybe there will be a change, or maybe not, but one thing [is] for sure, without accountability there will be little improvement.

An investigator who had been a member of a few IECs shared a similar opinion, he said:

The name Ethics Committee sounds like people on it know what they are doing. To tell you the truth, most people on the committee wouldn't know what informed consent is, but then how many people really know what it means to consent to something. But it is not only about consent, it is about whether the study is relevant and to who is it relevant, is it just for big-pharma?...I think those kind of issues are also relevant.

³⁷ See Indian Council for Medical Research (ICMR), Guidelines for preparing Standard Operating Procedures (SOP) for Institutional Ethics Committees for Human Research, available at http://www.icmr.nic.in/ethics_SOP.pdf (last accessed on June 2, 2018)

These perspectives show that ethics committees in India have not lived up to their functional requirements for quite some time now. These perspectives also help us understand why some scholars have suggested that the role of the IECs must include continuous monitoring of trials.³⁸ As one of my interviewees, quoted above, says “accountability” is important to ensure compliance with informed consent procedures.

7.3. CONCLUSION

Emily Sherwin has argued: “[i]t is in the nature of law that law can and must determine whether consent has occurred, even if no one is sure just what consent is.”³⁹ Informed consent is a heavily debated concept in ethics. Law has taken bits and pieces from these debates and defined legal standards to fix liabilities, which, as this chapter highlights, does not necessarily ensure ethical conduct. Moreover, most stakeholders have expressed their ambivalence regarding the force of law in addressing ethical issues in clinical research. This is where training in ethics is important. The ECs, the investigators, the clinicians, and everyone involved with clinical research, need to be adequately trained in research ethics. Ethically trained and aware researchers might go the extra mile in making sure that they receive understood and meaningful consent from participants. It is also important to stress that effective communication between the researchers and the participants is key to building relationships within which the goals of truly informed consent can be met. This chapter has also highlighted the problem of formalised ethics. This manner of operationalising ethics does not serve in protecting the autonomy of the research participant. This can partly be avoided if Ethics Committees step out of being a mere pre-clinical trial formality and ensure the protection of trial participant’s lives, their interests, and their autonomy. However, continuous monitoring by Ethics Committees is also not a complete solution because such monitoring requires manpower, training, time, and most importantly, a willingness on the part of EC

³⁸ U. M. Thatte & P. A. Marathe, *Ethics Committees in India: Past, present and future*, PERSPECTIVES IN CLINICAL RESEARCH, Vol. 8, Issue No. 1, (January-March, 2017), pp. 22–30.

³⁹ Although this quote is taken from the work of the author theorising consent in sexual relationships, it fits well in the context of informed consent. See E. Sherwin, *Infelicitious Sex*, LEGAL THEORY, Vol. 2. (1996), p 229.

members to perform such monitoring. Therefore, in the next chapter after formulating a grounded proposition based on the analysis of findings from this chapter and the previous one, I propose some innovative ways to regulate the conduct of researchers, based on my experiences in the field.

REFLECTIVE ANALYSIS AND SUGGESTIONS

8.0. Introduction

In this chapter I reflect on the data collection process and include my insights from that process to create a grounded proposition that will focus on practitioners' motivations to take informed consent. These insights, into what the process of informed consent on the grounds involves, are based on the data collected from my 'multi-stakeholder' sample size for qualitative inquiry and they stand in marked contrast to those outlined in the academic literature. While the latter largely focuses on how consent should be taken according to the essential features of consent as elaborated in Chapter 3, the former treats consent as just another step in the process of conducting scientific research. What emerges from my data is a picture that presents a situation where the process of informed consent is oftentimes followed neither as an ethical compulsion nor strictly as a legal obligation. It is not uncommon that researchers consider the process of consent as a mere procedural necessity, thereby performing the action without affording much consideration to either law or ethics. This often leads to apathy towards the 'larger cause' (or end goal) of informed consent which, I suggest, is a major reason for the misalignment between ethics, law and the practice of informed consent. To mitigate such misalignment I suggest the use of incentives and 'nudging' in addition to the more traditional forms of regulating conduct.

8.1. The Four General Perspectives on Informed Consent

Much has been written about the motivations of trial participants to volunteer for trials, but the motivations of stakeholders in taking informed consent has largely been ignored. If we are to desire the end goal of informed consent, which could be the protection of autonomy, the promotion of trust, the protection of research participants, or the prevention of abusive conduct, we must also be able to gauge what informs investigators' actions in taking consent. This is where the research findings of this thesis make a particular contribution towards scholarship in the field. This thesis adopted a phenomenological approach to uncover the ground realities of informed consent in practice. This involved uncovering different stakeholders'

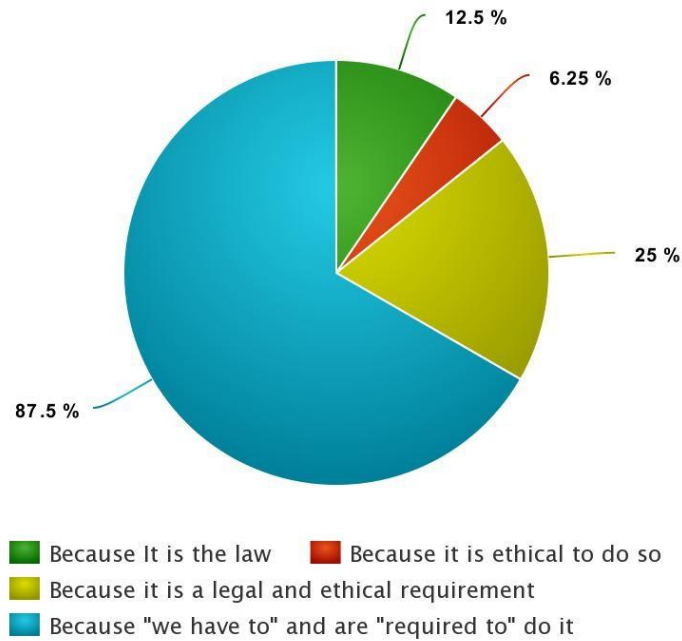
perceptions and experiences of dealing with informed consent in biomedical research in India. This approach to data collection uncovered some rather obvious iterations like “Yes! We follow all the informed consent rules as mentioned in the GCP and the ICMR Guidelines”, but also some tacit views on informed consent that point towards the possible motivations of the practitioners to take informed consent in research. These implied views on informed consent in practice can be categorised as follows.

My research findings derived from stakeholders’ views (predominantly the practitioners), reveal four general perspectives on informed consent. These are:

- i)** that while some regard it as an ethical obligation that ought to be observed;
- ii)** others consider it to be a legal compulsion (practiced with the intention to avoid lawsuits);
- iii)** and some even consider it to be both - an ethical and a legal necessity;
- iv)** nonetheless, the general view of the majority is one that perceives of informed consent as merely one of the many procedural requirements in the larger process of clinical trials (without giving any serious thought to either ethics or to the law).

Using excerpts from my interviews with researchers and by separating phrases that outlined their possible motivations to take informed consent, I condensed them into the four general perspectives, discussed above. These perspectives, if represented numerically, reveal the following pattern:

Four general perspectives on why informed consent is followed



There are some overlaps in the perspectives. Of the 16 current and ex-researchers/investigators interviewed, 2/16 researchers said that they followed informed consent (IC) because it was the law, 1/16 followed IC because it was ethical and the right thing to do, 4/16 said that IC has to be followed because it is a legal and ethical requirement, and 14/16 researchers used the words “required to”, “we have to”, “we must”, “it is one of the requirements”, “it is necessary for ethics approval”, and “it is thrust upon us”. It is important to note that not a single researcher said that they follow informed consent because it protects the autonomy of the participant, or that it somehow protects the research participants, or that it fosters trust, or any other justification for informed consent that figures in the academic literature. Thus, my data shows a contrast in the practical and academic understanding of informed consent

The aim of this thesis was to understand how the stakeholders viewed informed consent as opposed to how it is understood in the academic literature. The previous two chapters analysed this question by contrasting these views with the theory of informed consent. This revealed ambivalence by the different stakeholders about the role of law and ethics and how they perceive the force of both as affecting their actions. It might be that the ambivalence stems from weak regulatory oversight

and poor enforcement of law and the ethical guidelines. But my findings, particularly perspective **iv**) on informed consent, suggest that sometimes stakeholders do not apply the norms of informed consent in order to obey a law or by virtue of it being an ethical guideline; they do so because it is a formal requirement to proceed to the next step in clinical research. Most, if not all, are seldom concerned with the purpose or the goal of informed consent. I base this conclusion on two essential details:

- 1) Despite my interview requests put forward as “interview on informed consent in clinical research”, about 80-90% of my qualitative data includes stakeholders’ views on aspects of clinical research other than informed consent. The majority of my interview data touched upon issues such as the impact of patent laws on clinical research, pharmaceutical funding for trials, post-trial access to trial drugs, new regulations for clinical research in India, the need to restrict trials to public health needs, technical information on different phases of trials, the need for more home-grown trials appropriate for the genetic composition of the population, and so on. It took repeated and persistent questioning on informed consent for stakeholders to express their opinions on the topic. Either my interviewees thought that informed consent did not require as much attention as other pertinent issues in clinical research, or they genuinely had little to say about it, which leads me to the second important detail.
- 2) For most of the stakeholders that I interviewed, I had the impression that up until I asked questions on informed consent, they had barely given a thought to what informed consent purports to protect or achieve. But all the stakeholders were (rather too) quick to state that they duly took the informed consent of the participants and all the procedures were followed. Nearly all the stakeholders I interviewed possessed excellent knowledge about the procedural and ethical requirements for informed consent. Therefore, it becomes important to draw a distinction between someone possessing the knowledge about what informed consent entails and someone taking consent with the intention of fulfilling the purpose of informed consent. My research and fieldwork experience has led me to conclude that despite the enormous empirical literature in this field, academics have barely noticed that **the apathy towards the larger cause of informed**

consent is, perhaps, one of the causes for the lags between the theory and practice of informed consent. The reasons for this apathy could range from a personal lack of empathy to the effects of formalisation of ethics.

Therefore, while it is important to debate the ethical and legal theory of informed consent, it is also important to understand that informed consent is a continuous and dynamic process involving individuals who might not always have moral or legal reasons to perform actions. This important aspect has been ignored in much of the literature on informed consent; therefore, it gives rise to the central claim of the thesis which I elaborate in the next section.

8.2. Central Claim of the Thesis

The central argument of the thesis is that scholars and regulators need to acknowledge and understand the perceptions of stakeholders involved in the process of acquiring consent. My empirical research suggests that the practitioners show a degree of apathy to the goals of informed consent. This proposition does not only derive from their views on why they follow informed consent, as shown in the pie chart above, but also their views on a number of ethically debated positions pertaining to the essentials of informed consent, as outlined in Chapters 6 and 7.

Let us consider practitioners' views on voluntariness. The ethical understanding of voluntariness entails that a researcher has to ensure that a person consents to research participation without showing signs of coercion, undue influence, or any other controlling or restraining influences on her will. This leads to ethical debates on whether poverty compromises the autonomy of an individual, or whether incentives given to poor participants which they might not be in a position to deny, can be treated as coercive offers that render consent non-voluntary, hence invalid. These debates also include questions on whether a woman's decision-making ability or autonomy is compromised if she is dependent on her husband's consent to trial participation, and other such concerns. Despite the various ethical positions adopted by scholars on these debates (as outlined in Chapters 3, 6 and 7) the practitioners' views suggest that for them these are not real concerns. The researchers seem to consider factors like poverty, communitarian consent, dependence of women

on men or other elders in the family, and lack of adequate health care as *facts of life* in India and that these, by themselves, do not preclude a person from giving valid consent. This corresponds to the legalistic understanding of informed consent where consent is presumed to be voluntary unless otherwise so established and such factors are not legally recognised as factors that invalidate consent. Yet a majority of academic literature pertaining to informed consent in developing countries considers monetary payments to be undue inducement, poverty as coercive, communitarian consent as opposed to individual autonomy, and suggests ways to improve voluntariness in clinical research studies. If practitioners themselves do not think that something needs improvement or if some factors are not real concerns then the impact value of prescriptive academic work (i.e., work which prescribes the right methods to take informed consent from research subjects in different settings) in this direction is diminished. This also implies that any type of reforms in law and ethics that the academic literature presents will be meaningless if they are ignored or considered irrelevant from the stakeholders' perspectives.

As for information disclosure, the ethical understanding entails that all necessary information regarding a study would not only have to be disclosed by the researcher, but also understood by the participant. The practitioners, however, seem to think that conveying information in simple language and answering questions about the procedures are good indicators of information being understood. The practitioners that I interviewed did not use comprehension tests and thought that comprehension cannot be assessed even though they asserted that they made sure participants understood the information. The consent forms that I was shown during my fieldwork were elaborate and contained the necessary information regarding a study. Barring one researcher who used pictographic representation of the trial study (akin to a comic strip) no one else either had or showed me something that suited someone with a low (or no) educational background or thought that such an approach might be necessary. But most consent forms followed the ethical guidelines on the information a consent document ought to have. This too corresponds with the legal understanding of information disclosure which is silent on assessing comprehension but focuses on what needs to be disclosed. Yet a sizeable portion of academic literature focuses on "understood consent" and ways to achieve it. Here again, if

most practitioners are unconcerned about comprehension abilities or methods to attain such comprehension, it brings to question the ground impact of such prescriptive work.

As for ascertaining capacity to consent, the ethical approach is not limited to soundness of mind or age as the legal approach seems to be preoccupied with. The ethical understanding of capacity entails the ability to rationally assess the risks and benefits of a study and the consequences of one's decisions. However, the practitioners that I interviewed seemed to think that a person who appears to be of sound mind and is of major years has the capacity to consent. This too corresponds to a simplistic legal understanding of capacity. In fact, mental capacity tests are not legally mandated by any law in India (even for incapacitated individuals) and the researchers that I interviewed seemed to be content with equating capacity with age. Yet there is a good portion of the academic literature focusing on capacity assessment tests for both normal and incapacitated individuals. Such prescriptive work will also only be useful once the practitioners themselves value their usefulness.

In essence, the practitioners' views from my research suggests that they prefer the bare minimum approach to informed consent, i.e., just enough to box-tick the essentials of informed consent to avoid any legal trouble. Thereby indicating that they are only concerned with meeting legal formalities and not the spirit of the law. This seems to suggest that legalism is prevalent within clinical research in India. The more intensive approach, i.e., the ethical approach that keeps in mind the purpose and goals of informed consent does not appeal to most researchers. Perhaps this is because conducting clinical research in India is, in their own words, "a regulatory nightmare", "financially restricted", "extremely stressful", "time-bound", and "mostly not worth the time and effort put into it". This justifies the focus of academic literature on the ethics of clinical research in developing countries. However, the apathy towards the purpose and goals of informed consent leaves the gates open for unethical conduct. Often what is unethical is not illegal; therefore, if an act is performed for the sole purpose of it reaching the legality threshold, there is not much

room for new methods suggesting improvements on the act for the sole purpose of greater ethical compliance.

While my findings suggest problems, there is already awareness within the regulatory system of the need to improve on how informed consent is operationalised in practice. And the apathy towards the goal of informed consent can be overcome in a number of ways. Recall that one of my elite interviewees, an ICMR official, pointed at the dismal state of ethics training in India. Currently, this is an ongoing process in the country. The officials went on record to tell me that the training has improved drastically in the past decade, whilst conceding that there is much scope for improvement. Caught in a commercial model of scientific research where time is money and results have to be positive, practitioners/researchers barely think about questions of poverty, autonomy, voluntariness, capacity, etc., in their day-to-day trial-related work, let alone be indifferent towards them. If this is to be overcome, ethics training will need not only to inform researchers about what is ethical/legal conduct but they need more directly to be part of shaping the ethical debates that concern their domain. A good sign is that most people invested in biomedical ethics training in India are practitioners themselves, but there is still a long way to go before ethics training and ethical debates form an intrinsic part of the clinical research education.

Additionally, we have seen that in clinical research practice the legality of an act seems to be of greater consequence to researchers and research sponsors than ethicality. Therefore, courts, legislators, and regulators need to set clearer rules of procedure and redress mechanisms. It could be that the ambiguity in law also adds to the apathy towards informed consent. Often when we think that our actions will not be judged, we are bolder. Yet, the Indian context demonstrates that the fact of making certain unethical conduct illegal does not appear to prevent them. This truism does not negate the need for clarity in the law. Participants that have genuine grievances should be able to recover damages for harm caused to them by a lack of consent (beyond contractual compensation); therefore, there needs to be greater clarity on legal remedies available for such claims. I have given a few suggestions in Chapter 4 regarding this, but they are not exhaustive. The lack of informed consent

in research can be legally addressed in other ways and I welcome future legal research on this issue from a different lens than mine.

Yet another question comes to mind regarding this. What if after imparting ethics training and achieving clarity in law the apathy continues? This could be because actions borne out of reasons beyond the moral and the legal cannot be regulated solely by ethical and legal tools. In what follows I will analyse the actions of practitioners in the informed consent process and suggest some ways in which this query can be addressed.

8.3. Practitioner's action in the informed consent process

The Oxford English Dictionary defines a 'process' as "a series of actions or steps taken in order to achieve a particular end".¹ There are two primary actions involved in the interpersonal process of informed consent 1) the practitioner's action of taking informed consent from the research participant, and 2) the research subject's action of giving the consent to participate in a trial. Since the majority of the academic literature on informed consent deals with issues from the vantage point of research subjects, I have discounted action 2 and have addressed the issue from the viewpoint of the practitioner/investigator.

The motivation to perform an action is central to understanding why that act is not performed according to the ethical or legal standards. Although my research findings do not explicitly outline the motivations of practitioners to take informed consent, a few noticeable details are implicit in their ideas about informed consent and how some perceive the responsibility of taking consent as "thrust" upon them. As one investigator from a public hospital in Delhi said:

There are so many responsibilities and duties thrust upon us...administrative...procedural...often there are lapses and no one understands why there were lapses. We are always in the wrong.

¹ Oxford English Dictionary, (2nd edn., 1989). In a newer edition of the dictionary, process is defined as a "continuous and regular action or succession of actions occurring or performed in a definite manner, and having a particular result or outcome; a sustained operation or series of operations" (as the most common used no. 8), *see* "process, n.", OED Online, Oxford University Press, (January 2018). (Web last accessed on June 2, 2018)

We must bear in mind that an investigator in a trial is not only responsible for the consent requirement for the trial; she is also responsible for the entire procedure of the trial. This includes, but is not limited to, the medical care of trial subjects, compliance with the trial protocol, the responsibility of the investigational product(s), accountability for the trial site(s), and responsibility for all the records and reports related to the trial.² This entails that it would be unwise to assume that taking informed consent would be more important than all the other responsibilities placed upon the investigator. This could be a partial explanation for why my interviewees thought that informed consent was too “narrow” a topic for my research, as they saw informed consent as only a small part of what their jobs entailed and not even the most important part.

In Chapters 3 and 4 I maintained that law cannot guarantee ethical conduct because law, in general, prescribes the *minimum* acceptable standard of behaviour which is sub-par to the ethical vision of informed consent. I also maintained that the success of informed consent in research is largely based on the moral conduct of an investigator. Let me make it clear that when I use the term ‘law’, I mean law as it exists in typical legal systems and includes normative rules and guidelines that are generally made and enforced by institutions and authorities who are authorised to do so through the use of legal sanctions.³ By ‘morality’ I mean the rules that determine what is right or wrong and where moral incentives appear in the sentiments of virtue or guilt, and external moral sanctions are those of criticism and praise by others.⁴ Ethical guidelines, as are generally understood, lay out the ethical procedure for conduct, failure to adhere to which leads to professional or ethical misconduct. It is important to ascertain which of these prompt the investigators to follow informed consent because this knowledge could be used to ensure a better process of consent. I

² International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use, Good Clinical Practice (ICH GCP), Investigator, ¶ 4.1 – 4.13, available at <http://ichgcp.net/4-investigator> (last accessed on June 2, 2018)

³ To clarify this further, I am not using the social science perspective of the legal system or a pluralistic understanding of the law. I am using the above definition to include situations where the fear of legal sanctions induce compliance. That said, I am well aware of the empirical evidence that suggests that people do not obey the law just for the fear of sanctions.

⁴ See further S. Shavell, *Law versus Morality as Regulators of Conduct*, AMERICAN LAW AND ECONOMICS REVIEW, Vol. 4, Issue No. 2, (2002), pp. 227–257.

concede that there are overlaps between law, ethics, and morality, but here I will use them separately for the purpose of categorisation of motivational factors. Law has the ability to regulate conduct by motivating a person to do an action to avoid legal sanctions.⁵ Hence, there is a need for ‘unambiguous’ legal remedies for a lack of informed consent (as was argued in Chapter 4). Ethical guidelines can also regulate conduct by motivating a person to avoid the charge of professional or ethical misconduct. Individual morality governs the individual’s behaviour regarding what is right or wrong, but how do we understand actions borne out of the force of neither of these?

Let us consider the situation where a practitioner regards informed consent as just another procedural formality, the situation indicated in perspective **iv**) above. In such a situation, if there is absence of any other reason to perform an action, it can be argued that her actions towards the process of consent are not strictly borne out of moral or legal concerns. Law, ethics, and morality can give reasons for the actions of the individuals. But some individuals might not be guided by those reasons. Here, I must add the qualification that I am not judging the reasons why practitioners perform or omit to perform some actions. But I am aware that some academics might consider the acts of these few individuals as falling outside the Kantian theory of “doing the right thing for the right reason”.⁶ Therefore, regarding the actions of these individuals as lacking moral worth.⁷ While this by itself is a strong reason to focus

⁵ I’m aware of empirical evidence that shows that fear of sanctions is not the primary reason why people obey the law, but I am correlating it with the definition of law I propose above to reflect my research findings in an apt manner. *See generally* T. R. TYLER, *WHY PEOPLE OBEY THE LAW*, (Yale University Press, 1990).

⁶ This phrase derives from Kant’s theory that “it is not enough that it should conform to the moral law — It must also be done for the sake of the moral law”, meaning that an act must be borne out of duty, not some ulterior motive, to be moral. *See* M. J. SANDEL, *JUSTICE: WHAT’S THE RIGHT THING TO DO?* (Penguin, 2010), p. 111-116, while citing I. KANT, *GROUNDWORK FOR THE METAPHYSICS OF MORALS* (1785), translated by H. J. Paton (New York: Harper Torchbooks, 1964).

⁷ *Id.* SANDEL (2010). Here Sandel, while explaining Kant’s theory, says, “the motive that confers moral worth on an action is the motive of duty”. Further explaining Kant’s motive of duty, Sandel says that motive of duty means “doing something because it’s right, not because it’s useful or convenient”. Illustrating the point further, Sandel gives the example of people who are altruists and help other people out of compassion. Sandel explains that for Kant these actions are not wrong, but they lack moral worth because acting out of compassion is not the same as acting out of duty. If the altruist, owing to some misfortune, loses compassion for all humanity but continues helping others for the sense of duty, then his actions have moral worth. Therefore, while compassion is an ‘inclination’

on the motives of the practitioners, it does not help provide pragmatic solutions to situations where motives fall outside of pure reason (reason that is separate from empirical experience).⁸ Therefore, I have excluded Kant's theory on motives while presenting my analysis.

The important question that my data poses is - if the intent to perform the action of taking consent is neither born out of morality of the action and nor strictly from a legal obligation, how do we fix the action to achieve the desired end? Let us suppose that this end is protection of research participants through rigorous informed consent procedures. I propose that giving people the right incentives would help with informed consent where neither moral incentives nor legal sanctions seem to work. I also propose that the employment of the 'nudge theory', which so far has only been dealt with in terms of nudging patient choices, might be helpful in making researchers/investigators/practitioners more efficient in the performance of their actions towards securing informed consent of the participants. I suggest the use of these non-traditional forms of behaviour regulation as supplements to the more traditional forms, such as clear and unambiguous laws, strict regulatory oversight, better law enforcement, training and education, fostering desired attitudes within professional cultures, and so on. These non-traditional forms will be discussed in the following sections:

a) The Right Incentives

In most situations, law and morality are sufficient to regulate human conduct. But the formalisation of ethics, as evidenced in consent being reduced to a mechanical tick-box process, betrays the ideals of informed consent by making practitioners indifferent to the ideal. The action to take consent is performed, but without

to act morally, it is not a 'motive' acceptable to Kant. In this thesis, I am not judging the moral worth of the actions of the researchers, though I think that, Kant's theory in itself is a good reason to encourage dutiful behaviour amongst researchers. However, my interest in the reasons and motivations for the actions of researchers is relevant insofar as making recommendations to guide actions to ensure greatest protection of the research subjects.

⁸ For Kant, morality cannot be based on empirical considerations like desires, interests, or preferences of people at a given time as these factors are contingent and variable. For him these factors are inappropriate to serve as a basis for universal moral principles. Kant argues that morality based on interests and preferences cannot help us distinguish right from wrong, but can only help us become "better at calculation", See Sandel (2010) citing Kant, *supra* note 6, p. 106.

reflection on what it means and only because it is a formal necessity. The end goal for most practitioners is to have participants signify their consent (either in written or audio-video format). This is quite evident in the views of my interviewees. Even though some interviewees were aware that a proper informed consent process involves building a relationship with the research subjects, they were more concerned about meeting time constraints and other procedural formalities that inadvertently cut into the relationship building process. It must be kept in mind that clinical research is extremely time-consuming and expensive and researchers have responsibilities not only to keep the participants well informed but also to produce scientifically valid data (at the same time shouldering multiple administrative and miscellaneous duties).⁹ Within a strict time limit, some responsibilities end up taking more time and effort than the others, because of which some other responsibilities suffer. As one investigator at a research centre based out of Mumbai succinctly stated “we do as much is necessary and focus on other things that are more necessary for the trial”.

Going by the discussion on the content of informed consent in Chapter 3, if a researcher set down to achieve *perfectly* valid consent from a research participant, it would include:

- Ensuring voluntariness: this would entail that practitioners would need to conduct a thorough analysis of what motivates the individual sitting in front of them to volunteer for the trials. They would have to proceed only with those who possess ‘free will’ (which means that they are likely literate, not poor, and not influenced by doctor-patient, familial, or other relationships) and have the right motivations (the ethically agreed upon criteria of whatever falls under the ‘right’ motivations).
- Ensuring ‘proper’ and ‘adequate’ information disclosure and comprehension of information. This would mean, among other things, testing participant comprehension of technical and non-technical information or hiring experts who know how to assess comprehension - and redoing the entire process with

⁹ K. R. Chi, *Clinical research: Conducting a trial*, NATURE, Vol. 493, (2013), pp. 565-567.

other participants if some fell short on the ‘right level of comprehension’ criteria.

- Ensuring mental capacity based on agreed tests of reasoning capabilities, and ensuring that the participants have the ability to appreciate the situation and future consequences of their decisions, etc.

If researchers spent all their time trying to recruit participants by adhering to *all* the idealised requirements forwarded by scholars on informed consent, it could be very challenging to finish a trial within a stipulated time.¹⁰ As noted in the earlier chapters, there is no agreed-upon concept of voluntariness, no generally agreed test for comprehension, and no agreed-upon concept of reasoning ability. Considering the scholarly disagreements on these concepts and practical limitations, a minimum of these requirements is usually accepted as legally valid informed consent. Therefore, if one is to argue that researchers must strive for more and something closer to the ideal, one would have to recognise the need for incentives to attain that goal. This might not necessarily make the researcher intrinsically ethical but it might help in aligning her conduct to ensure a rigorous informed consent procedure.

Grant writes that incentives have long been used to achieve public policy objectives in the field of public administration.¹¹ She writes that the term ‘incentive’ is often and mistakenly used as a synonym for ‘reward’, ‘motivation’, or

¹⁰ It is important to mention that the commercialisation of biomedical research has imposed certain limits on researchers and biomedical research is not just ‘public-interest’ science anymore. It has been alleged that the commercialisation of research (despite increasing research activities) has contributed to the erosion of research ethics. This, though outside the scope of this thesis, is intrinsically linked to the conditions under which researchers perform trials. A sizeable proportion of researchers are weighed down by commercial interests while performing their duties. None of my interviewees spoke about the commercialisation of biomedical research, but I am mentioning it here for the reader to appreciate that time constraints (along with primacy of other interests) in biomedical research are very real. See generally S. KRIMSKY, *SCIENCE IN THE PRIVATE INTEREST: HAS THE LURE OF PROFITS CORRUPTED BIOMEDICAL RESEARCH?*, (Rowman & Littlefield Publishers, 2004); T. Caulfield, *The Commercialisation of Medical and Scientific Reporting*, PLOS MEDICINE, (December 28, 2004); N. Freemantle & D. Stockton, *The commercialization of clinical research: who pays the piper, calls the tune?*, FAMILY PRACTICE, Vol. 21, Issue No. 4 (2004).

¹¹ See generally R. W. GRANT, *STRINGS ATTACHED: UNTANGLING THE ETHICS OF INCENTIVES*, (Princeton University Press, 2011).

‘compensation’.¹² Grant and Sugarman define incentive as a particular kind of offer employed in a negotiation. According to them for an offer to qualify as an incentive, it must bear the following characteristics:

- 1) “the offer must be made as an extrinsic benefit or a bonus. It should neither be a natural or automatic consequence of an action nor a deserved reward or compensation;
- 2) the offer should be a discrete prompt expected to elicit a particular response;
- 3) the offer is usually made in the context of an authority relationship - for example, adult/child, employer/employee, government/citizen or government/organization; and
- 4) the offer is intentionally designed to alter the status quo by motivating a person to choose differently than he or she would be likely to choose in its absence.”¹³

Incentives are usually given by authorities to result in a desired action. If the desired action had resulted naturally or automatically, no incentive would be necessary. Incentives are considered as a form of power, but an alternative to other forms of power: persuasion and coercion.¹⁴ Coercion is, in most cases, objected to on ethical

¹² While distinguishing a reward from incentive, Grant notes that rewards are usually merited or deserved, and although an offer of a reward could be used as an incentive, rewards can also be given for past performances and do not necessarily function as incentives. Motivations could be internal or initiated by the individual, whereas incentives are regarded as “external prompts” to which an individual responds. Compensation is intended as redress for losses sustained in a situation, whereas incentives are designed to incite people to act in a particular way. See R. W. Grant & J. Sugarman, *Ethics in Human Subjects Research: Do Incentives Matter?*, JOURNAL OF MEDICINE AND PHILOSOPHY, Vol. 29, Issue No. 6, (2004), pp. 717–738. (Although this article views incentives from the viewpoint of research subjects, the first part of it deals with the meaning and ethics of incentives.)

¹³ *Id.*

¹⁴ GRANT (2011), *supra* note 11. Faden and Beauchamp define persuasion as “the intentional and successful attempt to induce a person, through appeals to reason, to freely accept—as his or her own—the beliefs, attitudes, values, intentions, or actions advocated by the persuader. Persuasion is always a non-clandestine form of interpersonal influence; the persuader openly puts forward reasons for accepting or adopting what is advocated.” Under persuasive techniques employed by an authority, all choices and actions performed by the persons are “non-controlled”. See R. R. FADEN & T. L. BEAUCHAMP, A HISTORY AND THEORY OF INFORMED CONSENT, (Oxford University Press, 1986), p. 262.

grounds,¹⁵ whereas persuasion is a weak instrument for situations where norm flouting is commonplace. The theoretical-practical misalignment in informed consent, as was elaborated upon in Chapters 3, 6 & 7, are proof that the desired action is difficult to achieve in practice. Therefore, as a proposition, the regulators and the government could consider giving researchers and research sponsors some *extrinsic* incentives (i.e., not part of emoluments owed to them as researchers but as those that are beyond their reach) to ensure that informed consent is not merely treated as a tick-box exercise. My suggestion is also based on years of management research that has proven that incentives work well in achieving desired changes in behaviour.¹⁶ More importantly, these are to be given as a supplement and not as a substitute to the traditional tools of behaviour regulation like that of stronger regulatory oversight and better implementation of existing laws and guidelines.

Giving the researchers the right incentives would perhaps bring about a change in the practice of informed consent. But what would the right incentive be in such a situation? Ethicists would consider right incentives as ones that are used in an ethically appropriate manner. It would be beyond my expertise and knowledge to suggest forms of incentives that would be able to affect a behavioural change. Moreover, the effect of incentives can be appraised only after they have been put into place. As such, there needs to be further research into what kinds of incentives would work. Subsequently there would be a need to empirically assess whether the chosen incentives bring about a change in the practice of informed consent. I am leaving this open to further scholarly enquiry.

Another reason that leads me to believe that incentives would work for affecting change in the process and practice of informed consent is that many

¹⁵ Coercion has been dealt from the perspective of the research subject in Chapters 3 and 6. Here I use coercion as a form of power when it is exercised by an authority. It is a controlling influence which means that the action occurring through coercion is completely controlled and non-autonomous. State/government authorities often employ coercion (legitimately) to make people comply with certain norms (e.g., income tax laws). Faden and Beauchamp opine that coercion “occurs if one party intentionally and successfully influences another by presenting a credible threat of unwanted and avoidable harm so severe that the person is unable to resist acting to avoid it.”, *Id.* p. 261.

¹⁶ D. D. Fehrenbacher, *An Integrative Framework of Influences on Behaviour Contributions to Management Science*, (Springer Berlin Heidelberg), pp. 13–29, in: D. D. FEHRENBACHER, *DESIGN OF INCENTIVE SYSTEMS: EXPERIMENTAL APPROACH TO INCENTIVE AND SORTING EFFECTS*, (Springer 2013).

stakeholders who I interviewed were quite ambivalent about law's role in assuring ethical conduct. The reasons they held this view included patchy law enforcement issues, the fear of arbitrary prosecution if criminal penalties were to be introduced and enforced,¹⁷ a lack of faith in the effectiveness of the legal system, and so on.¹⁸ The doubts expressed about the law's ability to bring about greater ethical compliance implies that legal coercion would not necessarily ensure proper process of informed consent. Moreover, assuming that *all* researchers *genuinely* take an interest in the promotion of rights, safety, and well-being of their research-subjects would be a bit of a stretch. The history and the present of biomedical research have multiple examples to the contrary. It seems that ethical guidelines and laws are not enough; therefore, I see value in offering some form of extrinsic benefit to spur the practitioner into ensuring proper informed consent from all the participants.

b) The Nudge

The nudge-theory rose to prominence in 2008 with the public release of Thaler and Sunstein's book, *Nudge: Improving Decisions about Health, Wealth, and Happiness*.¹⁹ Thaler and Sunstein defined their concept as:

A nudge, as we will use the term, is any aspect of the choice architecture that alters people's behavior in a predictable way without forbidding any options or significantly changing their economic incentives. To count as a mere nudge, the intervention must be easy and cheap to avoid. Nudges are not mandates. Putting fruit at eye level counts as a nudge. Banning junk food does not.²⁰

Choice architecture is the environment which influences people to make decisions.²¹ The choice architect can amend this environment without limiting the choices or forcing outcomes upon the individuals. Sometimes incentives are employed to nudge people into altering their behaviour but a nudge is much more than incentives.

¹⁷ M. Barnes, et al., *Clinical trial research is no crime*, THE HINDU BUSINESSLINE, (December 1, 2014), available at <http://www.thehindubusinessline.com/opinion/clinical-trial-research-is-no-crime/article6652150.ece> (last accessed on June 2, 2018)

¹⁸ The reasons are supplemented with verbatim quotes of practitioners in Chapter 6.

¹⁹ C. R. SUNSTEIN & R. H. THALER, *NUDGE: IMPROVING DECISIONS ABOUT HEALTH, WEALTH, AND HAPPINESS*, (Yale University Press, 2008)

²⁰ *Id.* p. 6.

²¹ SUNSTEIN & THALER (2008), *supra* note 19.

To further clarify the difference between a nudge and an economic incentive. An economic incentive might look like an 8-10% raise in the remuneration of an investigator in a sponsor-initiated trial²² for adhering to a more transparent and ethically sound informed consent procedure. In an investigator-initiated trial,²³ the incentive could include faster regulatory clearances upon proof that the informed consent procedure was sound throughout the trial. But a nudge would be more subtle, it would perhaps be in the form of letters circulated by the regulatory authorities saying something like “82% of investigators who appended a comprehension assessment reports along with the informed consent forms had faster rate of approval of their study protocol”, or something along those lines.²⁴ Nudges are intended to induce a cognitive effect that helps people make decisions that are ethically or socially desired. And something that appeals to the professionalism of researchers is intuitively likely to be more successful in such a high prestige industry.

Sunstein and Thaler formulated the concept of nudge from research that shows that certain changes in the choice architecture can influence the human cognitive system. For instance, anti-smoking labels and nutritional labels have helped people make better decisions regarding smoking and healthy eating. Similarly, Sreedhari Desai, an expert in organizational behaviour, has suggested that

²² A sponsor, which could be a pharmaceutical company or a biomedical research centre, initiates these trials. In such trials, investigators are hired as part of a larger team conducting the research. Sponsor-initiated trials (SITs) are large scale investments wherein economic incentives can work as a management strategy to increase efficiency, understood here as efficient taking of informed consent by investigators. Investigator-initiated trials (IITs) are studies initiated and independently managed by a non-pharmaceutical company researcher, like individual investigators or collaborative study groups or cooperative groups amongst different institutions. An external sponsor could fund the researcher, but in an IIT, the researcher is responsible for all the legal and regulatory responsibilities of the trial sponsor.

²³ *Id.*

²⁴ It could even be a letter by an authority stating “70% of clinical trials investigators think they should adopt norms x and y” or “80% of participants think investigators should give more information about the research trial”, etc, these of course have to be based on proper data. Such kinds of nudges work as peer or social pressure on people and they have proven to considerably affect people’s cognitive choices. See further R. B. Cialdini & N. J. Goldstein, *Social influence: Compliance and conformity*, ANNUAL REVIEW OF PSYCHOLOGY, Vol. 55, (2004), pp. 591-622.

ethical behaviour is encouraged by making people more *accountable* for their actions (like asking for an itemised receipt to avoid overbilling).²⁵

In public health situations, scholars have suggested the use of nudges to improve patient choices.²⁶ In the clinical research context, scholars have suggested the use of nudges to improve enrolment numbers for trials.²⁷ So far there has been no such study suggesting the use of nudges to make researchers more ethical while taking informed consent from participants.²⁸ This is most likely because the earlier concept of nudging mostly²⁹ applied to situations in which the harm intended to be reduced was harm done to self due to irrational decisions and not harm to others. However, new research on the applicability of nudges is not limited by scope. The research on the applicability of nudging in organisational behaviour, particularly for encouraging ethical behaviour, is still in its nascent stage.³⁰ Nudging has even shown

²⁵ S. D. Desai & M. Kouchaki, *Work-report formats and overbilling: How unit-reporting vs. cost reporting increases accountability and decreases overbilling*, ORGANIZATIONAL BEHAVIOR AND HUMAN DECISION PROCESSES, Vol. 130, (2015), pp. 79-88.

²⁶ A. Aggarwal, et al., *Nudge” in the clinical consultation – an acceptable form of medical paternalism?*, BMC MEDICAL ETHICS, Vol. 15, Issue No. 31, (2014).

²⁷ E. M. VanEpps, et al., *A nudge toward participation: Improving clinical trial enrollment with behavioral economics*, SCIENCE TRANSLATIONAL MEDICINE, Vol. 8, Issue No. 348, (2016). For instance, the authors suggested that the use of social norms which were both descriptive (i.e., what others are doing) and injunctive (i.e., what others approve of), could encourage participation in trials through a “safety in numbers” mentality. This mentality, they explained, worked like a friend’s recommendation for a restaurant or a long waiting list outside a restaurant. These served as social proof as they provided some form of normative information, and therefore, social norms could perhaps resolve anxiety about randomised controlled trials.

²⁸ Some researchers are already studying the effects of nudges on increasing scientific satisfaction so that the “transformative value of fundamental investigations can be increased without affecting the spirit of the basic research and scientists’ work satisfaction”, A. Ballabeni, et al., *Policies to increase the social value of science and the scientist satisfaction: An exploratory survey among Harvard bioscientists*, F1000RESEARCH, Vol. 3, Issue No. 20, (2014).

²⁹ I say mostly, not always, because one of the earliest examples of nudge was the etching of a housefly in men’s urinals at Schiphol Airport in Amsterdam to help men with “improving their aim”. Here the harm reduction did not necessarily imply harm to self, but to avoid causing a nuisance to others. Other popular examples of nudging, such as placing sugar-filled products on the lowest aisles in supermarkets or the use of calorie charts and health advice on junk food are all nudges that aim at harm reduction to self.

³⁰ There is a project being led by Professor Sreedhari and her colleagues on Ethical Nudges where they run field and Lab experiments to “investigate the role of ethical nudges, or non-coercive ways of leading people down moral pathways.” For instance, they found that displaying pictures of Mahatma Gandhi or other moral leaders triggered implicit psychological processes that made people feel averse to behaving unethically. Details of this project are available at, <https://ethics.harvard.edu/ethical-nudges> (last accessed on June 2, 2018)

promising results in changing behaviour of the health professionals, for instance, a recent UK study found that nudging could help reduce antibiotic prescription rates in an effort to reduce antibiotic resistance.³¹ A controlled trial was conducted where personally addressed letters, signed by the Chief Medical officer (as a trusted authority figure), were sent to about 800 GPs who were high antibiotic prescribers. The letter contained a social norm message (something like “80% practices prescribe fewer antibiotics than yours”) and highlighted some actions from the good clinical practices guidelines. The study showed a significant reduction in prescription rates in the trial cohort of the GPs.³²

The uses of extremely simple nudges, like the changing shelf level of foods with high calorie content to avoid notice, are mostly uncontroversial.³³ Such nudges are only persuasive and I am suggesting the employment of simple nudges to make researchers more compliant with proper informed consent procedures in biomedical research. This would arguably work to make the informed consent process feel less burdensome (psychologically) to the practitioners. If a nudge worked successfully, it could make researchers choose the option of building fruitful relationships with the research participants as default options.

³¹ M. Hallsworth, et al., *Provision of social norm feedback to high prescribers of antibiotics in general practice: a pragmatic national randomised controlled trial*, THE LANCET, Vol. 387, Issue No. 10029, (2016), pp. 1743-1752.

³² *Id.*

³³ Nudge-theory, as a tool for governance, has its fair share of detractors. Nudging is not, however, suggested in this thesis as a tool for public policy or as a large scale public governance strategy. See, for Sunstein’s response to his critics. C. Sunstein, *The Ethics of Nudging*, YALE JOURNAL ON REGULATION, Vol. 32, Issue No. 2, (2015) pp. 413-450; C. R. SUNSTEIN, WHY NUDGE? THE POLITICS OF LIBERTARIAN PATERNALISM (The Storrs Lectures Series), (Yale University Press, 2014); C. Sunstein, *There’s a backlash against nudging – but it was never meant to solve every problem*, THE GUARDIAN, (April 24, 2014), available at <https://www.theguardian.com/commentisfree/2014/apr/24/nudge-backlash-free-society-dignity-coercion> (last accessed on June 2, 2018); And here’s a list of articles criticising nudge as a tool for public policy - R. Baldwin, *From Regulation to Behaviour Change: Giving Nudge the Third Degree*, MODERN LAW REVIEW, Vol. 77, Issue No. 6, (2014), pp. 831-857; F. Mols, et al., *Why a nudge is not enough: A social identity critique of governance by stealth*, EUROPEAN JOURNAL OF POLITICAL RESEARCH, (2014); L. Will, *The politics of behaviour change: nudge, neoliberalism and the state*, POLICY & POLITICS, Vol. 42, Issue No. 1, (2014), pp. 3-19.

I am proposing that the research sponsors, the regulators, or the government could act as the choice architects for the researchers/practitioners. They could conduct tests on nudging researchers into acting more ethically by making use of the range of nudging tools. At this point, some might pose the objection that I am assuming that nudges would potentially work in India because they have worked in the US and UK, and that I am disregarding the vast differences in the contexts of these countries. The objection would be unfounded for two reasons: 1) nudges are designed based upon contextual research, and 2) nudges have proven to work in India.³⁴

It is important to note that nudges are *psychological* tools of behaviour regulation that are intended to influence the cognitive biases³⁵ associated with behavioural tendencies which are dependent on cognitive factors that determine how *most* people (as opposed to *all* people) behave. Behavioural scientists design specific nudges bearing in mind a certain population groups' cognitive biases. When I suggest that clinical research regulators in India could nudge research investigators into more ethical behaviour, I do not suggest simply transplanting similar nudges that have proven to work elsewhere. The kind of nudge that I am suggesting would have to be designed by behavioural researchers from scratch and would typically include a series of experiments.

Take, for instance, the nudges employed to reduce water consumption in Costa Rica. Behavioural researchers in Costa Rica designed several interventions to test the ones that worked best for achieving the desired result of reduced water consumption. Comparisons of water consumption with more proximate peer groups than those with a larger community were determined to be more effective within the targeted group. Thus, telling people that they use more water than their neighbours

³⁴ This is particularly true for nudges designed to reduce electricity, water, and gas consumption, but most recently nudges are being designed to tackle the problem of open defecation in the country. See A. Tagat & H. Kapoor, "*Sacred nudging*" and sanitation decisions in India, INDIA REVIEW, Vol. 17, (2018).

³⁵ A cognitive bias is often defined as a systematic pattern of deviation from rationality in judgement or norm. An individual's own subjective creation of social reality as opposed to the objective outlook determines their behaviour in the world, hence, leading to what is broadly called irrationality. see further A. Tversky & D. Kahneman, *Judgment under Uncertainty: Heuristics and Biases*, SCIENCE, Vol. 185, (1974), pp. 1124-1131.

was more effective in encouraging them to use less of it. However, telling them that they used more water than others in their city has negligible impact.³⁶

To find alternate ways of reducing electricity consumption, behavioural researchers in India found that employing nudging through school children was quite successful at influencing a family's cognitive bias to discount future gains. Future gains that accrue through saving electricity are usually disregarded by most households. Researchers found that an intervention at a community level with posters put up at apartments telling people that they saved more by "turning off the [electric] switch" was less successful when compared to an intervention involving children [from the same test site] being informed at school that saving electricity at home was better for the world.³⁷ Researchers found that when irrational needs or comforts are equated with the demands of off-spring, the latter get valued higher and are not easily discounted.³⁸

These examples show that in order to design nudges to achieve a desired result, behavioural scientists often formulate several interventions while considering the different variables that induce cognitive biases that make people act opposed to norms.³⁹ Some interventions prove to be more effective than others. It would be impossible to determine whether a nudge designed in a different setting has a chance of succeeding in another without carrying out evaluations on effectiveness.

Both incentives and nudging seem to offer the possibility of more effective regulation of informed consent procedures than the current ethical guidelines and stricter laws. Even so, I suggest the use of nudges only as a supplement to stricter implementation of guidelines and clearer remedial laws in order to achieve more

³⁶ S. Datta, et al., *Saving Water With A Nudge (Or Two): Evidence from Costa Rica on the Effectiveness and Limits of Low-Cost Behavioral Interventions on Water Use*, available at <https://www.isid.ac.in/~epu/acegd2015/papers/SaugatoDatta.pdf> (last accessed on July 28, 2018).

³⁷ A. Nayar & S. Kanaka, *A Comparative Study On Water Conservation through Behavioral Economics based Nudging: Evidence from Indian City "A Nudge in time can save nine"*, INTERNATIONAL JOURNAL OF BUSINESS AND SOCIAL SCIENCES, Vol. 8, Issue No. 11, (2017).

³⁸ *Id.*

³⁹ Designing of nudges involves experimenting with multiple variables that affect human behaviour in a given context, *see for example* S. J. Wu & E. L. Paluck, *Designing nudges for the context: Golden coin decals nudge workplace behavior in China*, ORGANIZATIONAL BEHAVIOR AND HUMAN DECISION PROCESSES, (October 31, 2018, in print);

long-term effects. Ascertaining the kind of nudge appropriate for this situation would require further psychological and behavioural research. Therefore, like incentives, I leave this open to further exploration.

8.4. Conclusion

The suggestions outlined in this chapter follow from the empirical data that suggests that researchers exhibit apathy towards the purpose of informed consent. Such apathy is one of the reasons why informed consent procedures have taken the problematic form that they have in India. To mitigate this apathy and to improve the informed consent procedures I have outlined a few suggestions that trail the possible motivations of the practitioner. If morality and ethics motivate a researcher then procedures followed by such researcher might become more efficient after rigorous ethics training. If the fear of legal sanctions is the sole motive then removing ambiguity from redress options, clarity in law, and efficient regulatory oversight of consent procedures might solve the problem of inadequate informed consent procedures. However, if neither of these are the motivating factors and there are other factors affecting researchers' actions or inactions while acquiring consent from the participants, other behaviour regulating tools like incentives and nudging might be able to achieve the desired informed consent procedures.

CONCLUSION

This thesis shows how the perceptions of practitioners and other stakeholders in clinical research deviate from how informed consent appears in the academic literature, which is dominated by ethical concerns. My empirical research findings hint at apathy towards the purposes and processes of informed consent. In the last chapter, I make a distinction between people who are knowledgeable about ethical standards and people who actually follow the ethical standards. In qualitative research such as this one, it is easier to make conclusions about the former than the latter. The perspectives accumulated in this research show what a handful of people from a community of thousands think. The first two chapters showed that there have been serious problems with informed consent procedures in clinical research in India. There was little to no regulation of clinical research prior to 2005. Even though regulation emerged after 2005, it was a bare minimum. It was only after the SAM case in 2012 that the regulations were tightened, but were slowly relaxed again to pacify the clinical research industry. The time frame of my research falls within the period where there was a suspicious atmosphere surrounding clinical research in India. The defensive attitudes and up-to-date knowledge on ethical standards from those who I interviewed were to be expected. However, one often learns more from what is not said, than what is. As I noted in Chapter 8, the *not much to say attitude* over informed consent is not a sign of engagement with informed consent for the purpose of fulfilling its goals. It is better seen as a sign of people who are resigned to ticking some boxes because that is what is required to conduct research and get the job done.

The Indian ethical guidelines on human subject research have existed since the 1980s, but violations have continued. The law has been slow to catch up to biomedical advancements. Most stakeholders (including regulators) that I interviewed seemed to think that stricter laws pertaining to informed consent were not necessary. Although they blamed poor law enforcement in India for their attitude, my research has suggested that this is also, partly, attributable to neither the researchers nor the regulators thinking much about the *purpose* of informed consent. In contrast to the stakeholder perspectives, the academic literature on informed

consent proposes a variety of ways to improve informed consent procedures, from mere tick-box-exercises to *understood* and *real* consent. However, most of the stakeholders that I interviewed, particularly the researchers, seem to be content with the procedures that they have been following and do not think much about informed consent in general.

The reality is that India has a huge population that is vulnerable due to poverty and a lack of access to health care. And even though such conditions do not by themselves vitiate consent, they are harsh situations that are facts of life in India. These harsh situations when combined with the high cost of litigation and a lack of a well-defined legal remedy, as shown in Chapter 4, make it easier for researchers to operationalise informed consent as the barest of procedures. A focus on legal solutions is unlikely to be enough to tackle the apathy. Which is why, if the legislature and regulators are content (as they seem to be) with the legal status quo pertaining to informed consent in India but still desire intensive procedures to portray that clinical research in India adheres to high ethical standards, they could opt to be choice-architects and nudge, or incentivise, the researchers into making ethical choices.

Beyond informed consent

In Chapter 2, while placing this thesis within a more global context, I intended for some findings of this thesis to be used by critical scholars in their works on the political economy of clinical research. While the research question that I sought to address was narrowed for the purposes of this doctoral research project, the research findings of this thesis can be further interpreted using different frameworks that add to the scholarship on global health and give intimations on law and Indian society in general. In the paragraphs that follow I will outline additional research areas that present a framework within which one could place the research findings of this thesis.

Liberalisation and its negative consequences are central to the scholarly critiques of global clinical research. The pharmaceuticalisation of society,¹ the quest for profit leading to structural violence for researchers and participants alike,² and the marketability of ethics (where commercial interests trump ethical interests)³ are the primary problems identified by social scientists. Scholars argue that bioethical processes like taking informed consent legitimise exploitative power rather than ensuring autonomous decision-making which adds to the structural violence perpetrated by the pharmaceutical industry.⁴

Scholars argue that following the spirit of neo-liberalisation the Indian government has shaped circumstances where sickness is being capitalised.⁵ There is plenty written about moving beyond informed consent as the hallmark of ethical clinical research and focusing on justice instead.⁶ Justice wherein drugs and vaccines are tried upon and made available to population that needs them.⁷ Justice for some Indian scholars would imply that clinical research in India should be carried out for

¹ Williams, et al. define pharmaceuticalisation as “the translation or transformation of human conditions, capabilities and capacities into opportunities for pharmaceutical intervention.” S. J. Williams, et al., *The pharmaceuticalisation of society? A framework for analysis*, SOCIOLOGY OF HEALTH & ILLNESS, Vol. 33, Issue No. 5, (2011), pp. 710–725

² A. Prasad, *Capitalizing disease: Biopolitics of drug trials in India*, THEORY, CULTURE AND SOCIETY, Vol. 26, Issue No. 5, (2009), pp. 1-29; K. Sunder Rajan, *Subjects of speculation: Emergent life sciences and market logics in the United States and India*, AMERICAN ANTHROPOLOGIST, Vol. 107, Issue No. 1, (2005), pp. 19-30; K. Sunder Rajan, *The experimental machinery of global clinical trials: Case studies from India*, in: A. ONG AND N. CHEN (EDS.), ASIAN BIOTECH: ETHICS AND COMMUNITIES OF FATE, (Durham NC: Duke University Press, 2010), pp. 1-55; K. SUNDER RAJAN, PHARMOCRACY: VALUE, POLITICS, AND KNOWLEDGE IN GLOBAL BIOMEDICINE, (Duke University Press, 2017), M. COOPER & C. WALDBY, CLINICAL LABOR: TISSUE DONORS AND RESEARCH SUBJECTS IN THE GLOBAL BIOECONOMY, (Duke University Press, 2014).

³ M. L. Flear, *Clinical Trials Abroad: The Marketable Ethics, Weak Protections and Vulnerable Subjects of EU Law*, CAMBRIDGE YEARBOOK OF EUROPEAN LEGAL STUDIES, Vol. 16, (2014), pp. 75-107; R. Jeffery, *War against disease without violence to clinical trial participants?*, in: S. CHANDRA (ED.), VIOLENCE-NONVIOLENCE ACROSS TIME, (Routledge, 2018); J. Fisher, *Expanding the frame of ‘voluntariness’ in informed consent: Structural coercion and the power of social and economic context*, KENNEDY INSTITUTE OF ETHICS JOURNAL, Vol. 23, Issue No. 4, (2013), pp. 355-379.

⁴ Prasad (2009); Sunder Rajan (2005, 2010, 2017), *supra* note 2.

⁵ *Id.*

⁶ See for example L. White, *Difference in medicine, difference in ethics? Or: When is it research or when is it kidnapping or is that even the right question?* in: P. W. GEISSLER & C. MOLYNEUX (EDS.), EVIDENCE, ETHOS AND EXPERIMENT: THE HISTORY AND ANTHROPOLOGY OF MEDICAL RESEARCH IN AFRICA, pp. 445-462, (Berghahn Books, 2011); J. P. KAHN, ET AL., BEYOND CONSENT: SEEKING JUSTICE IN RESEARCH, (Oxford University Press, 1998).

⁷ White (2011), *Id.*; Fisher (2013), *supra* note 3.

diseases that are prevalent in India.⁸ This would ensure that the drugs that are tested are relevant to the populations where the trials happen, as opposed to conducting trials for patients elsewhere. If we choose the framework of justice (if understood as conduct of and access to trialled drugs relevant to populations) for the findings of this thesis, the findings predominantly represent trials that were being done for products that were relevant to the Indian population. My interview data does not contain any information on whether the trial participants would have had access to the drug after the trial.

There is little statistical information on post-trial access to drugs being tried in India but plenty of research has been conducted on whether clinical trials conducted in India match the health care needs of the nation. A recent study evaluated trials registered with the Clinical Trials Registry of India (CTRI) between 2007 and 2015. In India's list of disease burden, the first rank has been continuously held by infectious and parasitic diseases that have the highest disability-adjusted life years (DALYs),⁹ but they accounted for only 5% of the total trials conducted in India and were ranked 7th according to number of trials. Cancer, that is ranked 6th on DALYs, ranks first in the number of trials conducted in India. With more such statistics, the authors of this study concluded that the greatest number of trials conducted in India pertain to non-communicable diseases which implies that "India is possibly contributing to global research but which may not entirely be necessary for the population and the health needs of the country."¹⁰ This repeatedly came up in the discussions that I had with some regulators, health activists, and investigators; they insisted on the need for more private sector trials for "diseases that affect our people".

⁸ V. Kamat, *Fast, cheap, and out of control? Speculations and ethical concerns in the conduct of outsourced clinical trials in India*, SOCIAL SCIENCE AND MEDICINE, (2014), pp. 48-55.

⁹ "One DALY is thought as one lost year of "healthy" life. The sum of DALYs across the population, or the burden of disease, can be thought of as a measurement of the gap between current health status and an ideal health situation where the entire population lives to an advanced age, free of disease and disability. DALYs for a disease or health condition are calculated as the sum of the Years of Life Lost (YLL) due to premature mortality in the population and the Years Lost due to Disability (YLD) for people living with the health condition or its consequences." See World Health Organisation (WHO), *Quantifying Burden of Disease from Mortality and Morbidity*, available at http://www.who.int/healthinfo/global_burden_disease/metrics_daly/en/ (last accessed 15/08/2018).

¹⁰ M. Chaturvedi, et al., *Do clinical trials conducted in India match its healthcare needs? An audit of the Clinical Trials Registry of India*, PERSPECTIVES IN CLINICAL RESEARCH, Vol. 8, Issue No. 4, (2017).

My findings show that most researchers whom I interviewed were aware of their roles as medical innovators and considered risks taken by research participants as risks taken for a better cause. This, however, must be understood within the larger pharmaceutical innovation context in India. Pharmaceutical innovation in India, as mentioned earlier, has not balanced out the public health needs of the nation. In fact the pharmaceutical innovation model has followed an “imitation to innovation” approach.¹¹ There have been some key regulatory triggers that shaped how pharmaceutical innovation turned out in India. The 1971 Patent Laws were led by public health concerns that encouraged imitation of expensive imported drugs that were inaccessible to the masses. The US Hatch-Waxman Act of 1984, that liberalised the US market for generics, provided an opportunity to the Indian generics producers to enter the global generics market. The manner in which Indian pharmaceutical innovation grew differs in many ways from the classic drug pipeline model of its Euro-American counterparts.¹² It makes for a fascinating study for those who study innovation, but for the purposes of this project it tells us that innovation in India has very recently come out of its imitation mode. This means that it lags behind in pharmaceutical innovation and particularly where this innovation would matter the most - to reduce the disease burden at home. Keeping this in mind perhaps the question to ask would be “are the risks taken by participants really for the greater good?”.

Coming to structural violence, a term coined by Galtung and supported by liberation theologians in the 1960s, which describes social structures, such as, economic, religious, legal, political, and cultural, that hinder individuals or societies (or groups) from reaching their full potential.¹³ Structural violence is usually “embedded in longstanding ubiquitous social structures, normalized by stable

¹¹ J. Chataway, et al., *Frameworks for Pharmaceutical Innovation in Developing Countries - The Case of Indian Pharma*, TECHNOLOGY ANALYSIS & STRATEGIC MANAGEMENT, Vol. 19, Issue No. 5, (2007).

¹² The controlled liberalisation route that India followed gave rise to a conservative and relatively slow velocity growth and innovation model. The pharmaceutical market in India is not simply a consumer market like its American counterpart, but it is a highly regulated space owing to the public pressure to keep drug prices low. Pharmaceutical innovation in India is mostly industry-led as opposed to research or health-service driven as in Brazil and Cuba, which perhaps also accounts for lesser focus on indigenous diseases and treatments. *See further* Chataway, et al, (2007), *Id*.

¹³ J. Galtung, *Violence, Peace and Peace Research*, JOURNAL OF PEACE RESEARCH, Vol. 6, (1969), pp. 167-191.

institutions and regular experience” and because they seem so unremarkable or ordinary in terms of how we understand the world, they are almost invisible.¹⁴ If we choose a framework of structural violence for the findings of this thesis, the complaints about time constraints, the pressure put on researchers for positive results, and the disgruntlement regarding more responsibilities “thrust” upon them, demonstrate that research investigators are arguably also victims of structural violence.

Commercialisation in clinical research has been supported by the Indian Government since 2005 and those with a Marxist or social ethos have been vocal about the ills of it.¹⁵ Sunder Rajan and Prasad have lamented the movement of biomedical research in India towards commercial testing, which has damaged a semi-socialist Indian pharmaceutical sector which once boasted of a vibrant generics industry that provided inexpensive drugs for the masses.¹⁶ For Sunder Rajan the biopolitics¹⁷ of commercialised clinical research is evident in the:

...violence of top-down, artifact-driven, technocratic imaginaries of public health that posed solutions to public health problems purely in terms of vaccines, without attending to epidemiological or infrastructural concerns and contexts within which the vaccines would be deployed.¹⁸

The commercialisation of research has put in place oppressive structures within which researchers/investigators have to conduct research. Clinical research is no longer wholly altruistic and with an increasing number of CROs, research has

¹⁴ In more general terms, violence is usually associated with something more physical. But for Galtung, violence is the “avoidable impairment of fundamental human needs or...the impairment of human life, which lowers the actual degree to which someone is able to meet their needs below that which would otherwise be possible” and. See J. GILLIGAN, *VIOLENCE: REFLECTIONS ON A NATIONAL EPIDEMIC*, (New York: Vintage Books, 1997), p. 306.

¹⁵ All authors in *supra* note 2.

¹⁶ *Supra* note 4.

¹⁷ Biopolitics, in the simplest of terms, can be understood as a political rationality which undertakes the administration of life and populations in order “to ensure, sustain, and multiply life, to put this life in order” and Biopower, which puts biopolitics to work, is a “power that exerts a positive influence on life, that endeavours to administer, optimize, and multiply it, subjecting it to precise controls and comprehensive regulations.” M. Foucault, *The Will to Knowledge: The History of Sexuality*, Vol. 1, (1976) (translated by R. Hurley, 1998), p. 137-138.

¹⁸ SUNDER RAJAN (2017), p. 70, *supra* note 2.

become factory-styled.¹⁹ The apathy towards the purpose of informed consent is possibly a by-product of working within structures which hinder the potential of the researchers to make ethical choices.

Certainly the two trial subjects interviewed for this research were victims of structural violence when they agreed to be part of a trial for money or medicine which they ought not to have needed in a society free from structural violence. But, as has been noted earlier, the sample size for this thesis was quite limited. The critical scholars who have worked on Indian clinical research issues have conducted ethnographic fieldwork for several years (a decade of ethnographic fieldwork in Sunder Rajan's case); and with the data they possess they are in more authoritative positions to explore issues of structural violence within the Indian clinical research paradigm.

Another aspect of critical scholarship that goes beyond informed consent pertains to the disenchantment with normative ethics. The critics of globalised clinical research have denounced normative ethics as having naturalised the consequential use of the experimental subject for capitalist value generation.²⁰ They argue that ICH GCP and GMP standards were methods through which the hegemony of Euro-American pharmaceutical industry was consolidated.²¹ All the research investigators and other stakeholders interviewed for this research were well-aware of the GCP and GMP standards, which shows that if the purpose of harmonisation of ethical standards was to consolidate such hegemony, it seems to have worked.

Sunder Rajan has charted the different ways (ICH GCP standards being one) through which the Euro-American pharmaceutical industry "operates to institute forms of governance across the world that are beneficial to its own interests".²² But it is not only instituting forms of governance, but also implanting the idea that a country's pharmaceutical progress depends on their support is what really

¹⁹ See also I. R. Baker, *Has the commercialisation of medical research gone too far*, INTERNATIONAL JOURNAL OF RESEARCH IN MEDICAL SCIENCES, Vol. 3, Issue No. 10, (2015).

²⁰ SUNDER RAJAN (2017), p. 106, *supra* note 2.

²¹ "I argue that the global harmonization of clinical trials and intellectual property regimes must be understood in terms of this expansion of multinational corporate hegemony", SUNDER RAJAN (2017), p. 7, *supra* note 2.

²² SUNDER RAJAN (2017), p. 6, *supra* note 2

consolidates the hegemony. Some investigators I interviewed were worried about the “data scandals” that have hit Indian CROs wherein some CROs were found to have falsified data for the purposes of regulatory approval by the Euro-American authorities.²³ They worried that “if trust is broken with the foreign regulators and companies...who will come here?”. While some other investigators wanted to have clinical research experience with Euro-American sponsors because that would help their research profile “greater than working on India-specific trials”.

If we were to contextualise the findings of this thesis within the more general field of law and society, the apathy shown by researchers towards the ethical aspect of informed consent (or to the purpose of it) could resonate beyond just informed consent. Of course, the apathy shown to informed consent could also stem from reasons beyond the ones that I have identified. Here I address the complaints of the researchers which hint at over-commercialisation of biomedical research as a potential reason for the apathy. It could also be that similar apathy is found in other fields towards other legal and ethical principles. The interview excerpts calling court decisions as pyrrhic victories, regulators being wary of legal solutions, a general acceptance that legal enforcement in India is patchy, the industry complaints of overregulation hindering innovation, could perhaps be replicated in other fields using a similar multi-stakeholder approach to data collection. There are indeed insinuations to the relationship between law and the Indian society in this thesis, but it could be taken further in future research with a different research question and a larger sample size.

All the frameworks discussed afore are vital to acquiring a comprehensive picture of clinical research in India and also more globally. In essence, the pharmaceutical industry and people who are a part of it, in this case the researchers/

²³ M. Mezher, *WHO: ‘Critical’ Data Integrity Issues Found at Indian CRO*, REGULATORY FOCUS, (July 7, 2015), available at <https://www.raps.org/regulatory-focus%E2%84%A2/news-articles/2015/7/who-critical-data-integrity-issues-found-at-indian-cro> ; P. Raghvan, *US Food and Drug Administration issues data integrity notice to Indian CRO Semler*, THE ECONOMIC TIMES, (April 22, 2016), available at <https://economictimes.indiatimes.com/industry/healthcare/biotech/pharmaceuticals/us-food-and-drug-administration-issues-data-integrity-notice-to-indian-cro-semler/articleshow/51935137.cms> ; D. Lowe, *Getting the Indian Drug Scandals Straight*, SCIENCE TRANSLATIONAL MEDICINE, (January 6, 2016) available at <http://blogs.sciencemag.org/pipeline/archives/2016/01/07/getting-the-indian-drug-scandals-straight> (all links last accessed August 15, 2018)

investigators, are caught between two often opposing forces – legal and ethical regulations and the market. For investigators, this means that on the one hand they have the ethics of medical research and on the other hand they have the market imperatives of efficiency and effectiveness. In order to perform a balancing act between the two, we have principles like informed consent that allow research to be conducted, but only with the *free choice* of a research participant. Therefore, assuming that the current commercialised structure of clinical research will remain in place for a long time to come, informed consent (if done right) is our best bet to ensure that the past abuses of experimentation on humans are not repeated.

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Appendix I

IN THE SUPREME COURT OF INDIA

CIVIL ORIGINAL JURISDICTION

WRIT PETITION (CIVIL) NO. _____ OF 2012

IN THE MATTER OF:

1. Swasthya Adhikar Manch,
Indore (M.P.)
Through its Convenor
Chinmay Mishra
6, Bijasan road,
Opposite Mahavir Bagh,
Indore, Pin- 452005
Mob- 9893278855

Petitioner no. 1

2. Amulya Nidhi
Co-Convenor
Swasthya Adhikar Manch,
Indore (M.P.)
22, Shanti Nagar,
Sri Nagar Extension,
Khajrana Road,
Indore, Pin- 452001
Mob- 942531547

Petitioner no. 2

Vs.

1. Ministry of Health and Family Welfare
Through its Secretary,
Government of India
Nirman Bhawan, New Delhi

Respondent No. 1

2. Central Drugs Standard Control Organisation
Through Director General of Health Services
Government of India
FDA Bhavan, ITO,
Kotla Road,
New Delhi -110002

Respondent No. 2

3. The Drug Controller General of India
Through Director General of Health Services
Government of India
FDA Bhavan, ITO,
Kotla Road,
New Delhi -110002

Respondent No. 3

3. Medical Council of India,
The Chairperson
Pocket 14, Sector 8,
Gurgaon, Haryana

4. State of Madhya Pradesh
Through its Chief Secretary,
GoMP, Vallabh Bhavan,
Bhopal (M.P.)

Respondent No. 5

A WRIT PETITION UNDER ARTICLE 32 OF THE CONSTITUTION OF INDIA

To,

The Hon'ble Chief Justice of India
and his Lordships Companion Justices
of Supreme Court of India

The humble petition of the Petitioner abovenamed

Most Respectfully Showeth:

(I) This Writ Petition has been filed under Article 32 of the Constitution to appraise this Hon'ble Court about the illegal and unethical clinical trials conducted on adults, children and even mentally ill persons in this country. These trials are conducted in India either because these trials are not allowed outside India or because such trials are cost prohibitive in the country of origin. Further, the poor, illiterate and vulnerable sections of the society become subjects of these illegal clinical trials. In conducting these trials, the doctors, with the sole aim of making money, grossly compromise with ethical medical practices. These trials are conducted without regard to the consent of the subjects, despite apparent conflicts of interest. The petitioners submit that the manner in which these trials are conducted is grossly illegal and violative of Article 21 of the Constitution. The inaction of the Government in not banning / restricting these clinical trials is violative of Article 14 of the Constitution. The issue of clinical trials is raised in the Rajya Sabha, Vidhan Sabha of Madhya Pradesh, Economic Offences Wing (EOW) Madhya Pradesh and in several study reports/magazines/journals/newspapers etc. The Government has still not taken any action regarding this extremely

which is nothing but a scam. Therefore, the present Writ Petition is filed in public interest.

IA. That the petitioners had approached the concerned authorities, including the respondents no. 1 & 2 as indicated in Annexure P-15 Colly (Vol-IV- Pages 820 to 843) in relation to the reliefs that the petitioners are praying for in the present petition, however there has been no action taken or no relief been granted by any of the authorities till date.

(II) BRIEF FACTS OF THE CASE:

1. The Petitioner, Swasthya Adhikar Manch (SAM) is a network of individuals and organizations working in Madhya Pradesh and other parts of India on issues related to health & health rights. The Petitioner is not a registered organization but an unregistered Association. The objective of 'Swasthya Adhikar Manch' is to create awareness on health issues, patient rights and health rights through various means and to provide legal support to people in case of violation of these rights. It organizes awareness programmes, expert lectures and publishes material like posters, pamphlets, booklets etc. The members of this network are mainly health experts, doctors, health activists and social workers and journalist working on health and social issues since many years.

Mr. Chinmay Mishra is a social activist and also an executive editor of Sarvodaya Press Service, Indore. Sarvodaya Press Service, is a platform to publish articles on current social issues. Through Sarvodaya Press Service, other newspapers and periodicals. Mr. Chinmay Mishra has written and edited many articles on health and livelihood rights etc. He has also edited a

Various individuals and organizations which form part of the network are Mr Amulya Nidhi, impleaded as Petitioner No.2, a health activist working on issues of health rights in Madhya Pradesh and other parts of country. He is also working group member of Jan Swasthya Abhiyan (People's Health Movement). He has also written articles, booklets on health and livelihood issues and actively involved with various social groups in India. He is also the co-convenor of the Swasthya Adhikar Manch.

Mr. Vijay Chaudhary is a Senior journalist and chief reporter of 'Patrika', a leading Hindi newspaper in the state of Madhya Pradesh.

Ms. Belu George, lawyer and Rajendra Bajode are active and founder members of the organization "Juggi Basti Sangharsh Morcha, Indore" which is working on issues of urban poor since 18 years. It is mainly focusing on issues of housing rights, education, health & livelihood protection for the rights of the urban poor.

2. That this Writ Petition is concerned about the clinical trials that are conducted on human beings for introducing new drugs in the market. Before elaborating on the subject-matter of this writ petition, it is necessary to know what these trials are and why and how they are conducted in India.

3. That whenever a new drug is introduced by a Drug Company for use by human beings, it is necessary to conduct clinical trials in

Cosmetics (2nd Amendment) Rules, 2005. This definition under Rule 122DAA of the Rules reads as follows:

"Rule 122DAA: Definition for the clinical trial.- *For the purpose of this Part, "Clinical Trial" means a systematic study of new drug(s) in human subject(s) to generate data for discovering and/or verifying the clinical pharmacological (including pharmacodynamic and pharmacokinetic) and/or adverse effects with the objective of determining safety and/or efficacy of the new drug."*

True and correct copy of the relevant provisions of the Drugs and Cosmetics Act, 1940 (hereinafter referred to as the Act of 1940, as amended) and the Rules, 1945 as amended in 1988 and 2005 (hereinafter referred to as the Rules of 1945, as amended) are filed as Annexure P-1 (Colly)(Pages 92 to 184).

4. That before going into the complexity of the issue of 'Clinical Trials', and the legal regime under which they are conducted, the Petitioners deem it proper to mention below, the stages of clinical trials.

To begin with, a New Chemical Entity (NCE) or a new drug is generally discovered by a drug company in their laboratory. It then undergoes the following stages of testing:

- **Pre-clinical Trials** are conducted on animals such as rats, mice, guinea pigs, dogs and rabbits. These studies are done in great detail to determine the toxicity, absorption, distribution, metabolism and excretion of the drug. In these studies effect on fertility, etc.

(b) Pharmacokinetics, i.e., characterization of a drug's absorption, distribution, metabolism and excretion. Although these studies continue throughout the development plan, they should be performed to support formulation development and determine pharmacokinetic parameters in different age groups to support dosing recommendations.

(c) Pharmacodynamics: Depending on the drug and the endpoints studied, pharmacodynamic studies and studies relating to drug blood levels (pharmacokinetic/pharmacodynamic studies) may be conducted in healthy volunteer Subjects or in patients with the target disease. If there are appropriate validated indicators of activity and potential efficacy, pharmacodynamic data obtained from patients may guide the dosage and dose regimen to be applied in later studies.

(d) Early Measurement of Drug Activity: Preliminary studies of activity or potential therapeutic benefit may be conducted in Phase I as a secondary objective. Such studies are generally performed in later Phases but may be appropriate when drug activity is readily measurable with a short duration of drug exposure in patients at this early stage.

- **Stage II Testing (Therapeutic Exploratory Phase):**

- (i) The primary objective of Phase II trials is to

generally non-clinical and are essential pre-requisite before clinical trials are conducted on human subjects.

After conduct of Pre-Clinical trials on animals a drug under goes a **four stage clinical trials** on human beings. The clinical trials undergo the following 4 phases, as provided in Schedule Y of the Rules of 1945.

- **Stage- I (Human Pharmacological Phase) –**

- (i) The objective of studies in this Phase is the estimation of safety and tolerability with the initial administration of an investigational new drug into human(s). Studies in this Phase of development usually have non-therapeutic objectives and may be conducted in healthy volunteer subjects or certain types of patients. Drugs with significant potential toxicity e.g. cytotoxic drugs are usually studied in patients. Phase I trials should preferably be carried out by Investigators trained in clinical pharmacology with access to the necessary facilities to closely observe and monitor the Subjects.

- (ii) Studies conducted in Phase I, usually intended to involve one or a combination of the following objectives:-

(a) Maximum tolerated dose: To determine the tolerability of the dose range expected to be needed for later clinical studies and to determine the nature

short-term side-effects and risks associated with the drug. Studies in Phase II should be conducted in a group of patients who are selected by relatively narrow criteria leading to a relatively homogeneous population. These studies should be closely monitored. An important goal for this Phase is to determine the dose(s) and regimen for Phase III trials. Doses used in Phase II are usually (but not always) less than the highest doses used in Phase I.

- (ii) Additional objectives of Phase II studies can include evaluation of potential study endpoints, therapeutic regimens (including concomitant medications) and target populations (e.g. mild versus severe disease) for further studies in Phase II or III. These objectives may be served by exploratory analyses, examining subsets of data and by including multiple endpoints in trials.

- (ii) If the application is for conduct of clinical trials as a part of multi-national clinical development of the drug, the number of sites and the patients as well as the justification for undertaking such trials in India shall be provided to the Licensing Authority.

- **Stage III Testing (Therapeutic Confirmatory Phase):**

- (i) Phase III studies have primary objective of demonstration or confirmation of therapeutic benefits(s). Studies in Phase III are designed to

These studies should be intended to provide an adequate basis for marketing approval. Studies in Phase III may also further explore the dose-response relationships (relationships among dose, drug concentration in blood and clinical response), use of the drug in wider populations in different stages of disease, or the safety and efficacy of the drug in combination with other drug(s).

- (ii) For drugs intended to be administered for long periods, trials involving extended exposure to the drug are ordinarily conducted in Phase III, although they may be initiated in Phase II. These studies carried out in Phase III complete the information needed to support adequate instructions for use of the drug (prescribing information).
- (iii) For new drugs approved outside India, Phase III studies needs to be carried out primarily to generate evidence of efficacy and safety of the drug in Indian patients when used as recommended in the prescribing information. Prior to conduct of Phase III studies in Indian subjects, Licensing Authority may require pharmacokinetic studies to be undertaken to verify that the data generated in Indian population is in conformity with the data already generated abroad.
- (iv) If the application is for the conduct of clinical trials

should be provided to the Licensing Authority along with the application.

- **Stage IV (Post Marketing Trial):**
- Post Marketing trials are studies (other than routine surveillance) performed after drug approval and related to the approved indication(s). These trials go beyond the prior demonstration of the drug's safety, efficacy and dose definition. These trials may not be considered necessary at the time of new drug approval but may be required by the Licensing Authority for optimizing the drug's use. They may be of any type but should have valid scientific objectives. Phase IV trials include additional drug-drug interaction(s), dose-response or safety studies and trials designed to support use under the approved indication(s), e.g. mortality/morbidity studies, epidemiological studies etc.

It is necessary to point out that Stage 1 and Stage II trials are considered to be serious or risky in nature, and the Trial Stages III and IV commence when it is confirmed that the drug is safe and effective as intended medication for the purpose of marketing. The clinical trial of Stages I and II have to be conducted with extreme caution and should be under continuous supervision as they have a direct impact on human beings, their health and life in general. It must also be noted that the Stage I and II trials can be conducted only after pre-clinical trials are done on animals. There ought to be clear guidelines and precautionary measures commencing from pre-clinical trials up to stage IV trials. The details of the ...

where they lack protection. The petitioners will also point out complete lack of safeguards and monitoring resulting in violation of right to health and life.

5. That after the establishment of the 'Trade Related Aspects of Intellectual Property Rights' (TRIPS) regime, under the WTO 'product patents' are granted protection by all countries who are the members of WTO. To bring the Patent Act, 1970 in accordance with the requirements of TRIPS, 'product patents' have been introduced in place of 'process patents'. This amendment has given a big advantage to multinational and large pharmaceutical companies who are already holding 'product patents' in their favour. The race among the pharmaceutical companies is to market their product patent as early as possible in order to derive maximum advantage in capturing markets in the developing/third world countries. The only hurdle which they have to cross is to ensure that the new drug undergoes clinical trials for market approval, in particular Stage I and II trials. This brief background, which will be elaborated further, is necessary to understand genesis of the problem.
6. That the petitioners submit that Part XA pertaining to "Imports or manufacture of new drug for clinical trials or marketing" i.e. Rule 120A to 120E were added vide G.S.R. 944 (E) dated 21.9.1988 in the Drugs and Cosmetics Rules, 1945, along with Schedule Y. The Rules of 1945 did not provide for conducting clinical trials in India. The consequences of this amendment in 1988 were that:

- The details of importing and testing of the drugs were provided in a newly introduced schedule Y.
 - Phase I, II and III trials were permitted in the country.
 - // However, Phase I & II trials were permitted with certain restrictions and a phase lag was introduced which implied that for conducting Phase II Drug Trials in India, Phase III trial data from other countries must be available which in effect meant that Phase II trials could be conducted in India only if Phase III trials had been completed abroad. //
 - Similarly Phase III trials were allowed only if the drug was being marketed abroad.
7. That the Drug and Cosmetic Rules, 1945 were again amended in January, 2005 (Notification GSR 32(E) dated 20.01.2005) to make the conducting of clinical trials easier. The Phase lag was removed and gave way to concurrent multi-country trials. The removal of Phase lag 'significantly reduced the phase development time' which was pro-industry step as it allowed faster drug development. However, the "Phase Lag" was centric to the safety of subjects and as a consequence of this amendment, the risk to subjects has increased. As a result of the amendment in 2005, the restrictions on the number of patients and Centers in Phase I & II were removed. This aspect has been dealt with in many journals/periodicals by the experts.
 8. That the relevant provisions under the Rules (as amended up to date), are Rule 21(b) which defines the term "licensing authority"

122B, 122D, 122DA, 122 DAA, 122 DB, 122 DC, and 122E. These Rules have to be read with Schedule Y. The said Schedule refers to Appendix I to Appendix XI. Schedule Y mentions about application for permission, clinical trial, responsibilities of sponsors, responsibilities of investigators, informed consent, responsibilities of the ethics committee etc. Appendix I provides for the data which has to be submitted along with the application for conduct of clinical trials and Appendix II refers to the structure, contents and format for clinical study reports. After receiving this study report, the licensing authority grants permission. Rule 122 A & B authorizes the licensing authority to seek further information in case the data provided or generated is "inadequate". Therefore, the only power which has been given to the licensing authority is to look into the adequacy of the material. The licensing authority cannot refuse permission if it is not in public interest or the data has been generated or trial has been conducted in violation of Schedule Y and the Appendix i.e. Rules in general. This is a very serious lacuna in the provisions and is resulting in grant of permissions by total non application of mind even when the provisions of law have not been complied with while conducting the trial.

9. That under the Rules of 2005, before granting approval for conducting clinical trial, Ethics Committee has to review the following documents (as per Appendix -VIII), but these documents are rarely available and/or reviewed by the Ethics Committee. The review of following documents is necessary

- (a) Trial Protocol (including protocol amendments), dated Version No.(s).....
- (b) Patients Information Sheet and Informed Consent Form (including updates, if any) in English and / or vernacular language.
- (c) Investigator's Brochure, dated....., Version No.....
- (d) Proposed methods for patient accrual including advertisement(s) etc. proposed to be used for the purpose.
- (e) Principal Investigator's current CV.
- (f) Insurance Policy/Compensation for participation and for serious adverse events occurring during the study participation.
- (g) Investigator's Agreement with the sponsor.
- (h) Investigator's Undertaking (Appendix VII)

10. That Domestic Guidelines governing clinical Trials were brought out by the Indian Council of Medical Research (ICMR), namely, 'Policy Statement on Ethical Considerations Involved in Research on Human Subjects' in 1980. They later revised these guidelines in 2000 as the 'Ethical guidelines for Biomedical Research on Human Subjects'. Further, in October, 2006 the Director General ICMR published revised guidelines in the name of 'Ethical Guidelines for Biomedical Research on Human Participants' and this was referred to as the '**ICMR Code**'. It carries statements of General Principles and Special principles on research and is a reiteration of the international established principles on the subject. The *general principles* lay down that:

- No person should become a mere means for betterment of others, scientific experiment should be consistent with his/her dignity, and should not be subjected to grave risks,
- Research must be subjected to a regime of evaluation and
- It must ensure saving of each human life as an end in itself.

The *specific principles* specifically discuss clinical trials in context of the introduction of schedule Y and lays down very elaborate guidelines for Ethics Committees, Informed Consent, Compensation for Participants, Conflict of Interest, Selection of Special Groups for research, Post Trial Access etc. True and correct copy of the Ethical Guidelines for Biomedical Research on Human Participants, 2006 is filed as Annexure P-2 (pages 185 to 304)

11. That the 'GCP Guidelines for Clinical Research in India' were issued by the Central Drug Standard Control Organization (CDSCO), an organization headed by Director General of Health Services, Ministry Of Health and Family Welfare, Government of India. It lays down the quality standards for designing, conducting and recording Clinical Trials. After endorsement by the Drug Technical Advisory Board (DTAB) these were adopted by the Government of India in 2001. They discuss the essential elements of trial protocols, quality considerations, data maintenance procedures, audits, publications, evaluation and also ethical considerations etc. True and correct copy of GCP Guidelines for Clinical Research in India dated nil is filed as Annexure P-3 (pages 305 to 404) respectively.

Identification of doctors, and the consent taken from the patients/persons (trial subjects) is an area where rampant violations, unethical practices, and exploitation of subject trials takes place. Throughout the entire process of clinical trial, it is the financial aspect that dominates, and human beings, particularly the poor and those vulnerable are used as guinea pigs. The petitioners are enclosing a power-point presentation by Dr. Chander.M.Gulathi, Editor, Monthly Index of Medical Specialities (MIMS) which highlights the legal aspects, illegalities, unethical practices, violations dated nil as Annexure P-4 (pages 405 to 421)

INTERNATIONAL SCENARIO:

13. That world-over the subject of clinical trials is considered to be an important ethical issue as it not only touches animal life, but the welfare of human beings and their rights. The Rules of 1945, as amended also refers to the international regime, in particular the Helsinki Declaration, 1964. The international instruments/declarations are as follows.
- 13.1. The evolution of International norms regarding clinical trials has risen through the following path: Subsequent to the tragedy of human experimentation by the Nazis during the World War, the *Nuremberg Code* was developed in the course of the Nuremberg Trials. Among other things, this code lays down that:

- The voluntary informed consent of the human subject is absolutely essential.

- There should not be any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion.
- The subject should have sufficient understanding on the subject matter involved to make an informed decision.
- The subject should know the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonable to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

13.2. **The Helsinki Declaration, 1964 (last amended in 2008)** of the World Medical Association and the *International Guidelines for Biomedical Research Involving Human Subjects*, 1993 by WHO-CIOMS (Council for International Organizations of Medical Sciences) elucidate certain principles which are essential during Clinical Trials:

- Selection of subjects must be fair and based on sound scientific principles. Advantage of economic and medical vulnerability should not be taken.
- The Doctor should act only in the interest of the patient i.e. risk to the patient should be minimized and benefit enhanced. There must be respect for the enrolled subject- their well being should be monitored and must have an opportunity to withdraw.

research, the physician must seek the consent of their legally authorized representative.

- The research must be reviewed independently and terminated if harming or not benefiting the patient.
- After conclusion of research best possible treatment should be accessible to the patient.

True and correct copy of The CIOMS-WHO International Ethical Guidelines for Bio-Medical Research Involving Human Subjects, 2002, and The Declaration of Helsinki, 1964 (last amended in 2008) is filed as **Annexure P-5 (Pages 422 to 512 and P-6 (pages 528 to 534).**

13.3. That aside from these specific guidelines dealing with experimentation on human subjects, there are general principles under the human right regime which are as follows:

- In the **Universal Declaration of Human Rights, 1948** (adopted by the General Assembly of the United Nations) concerns are expressed about rights of human beings being subjected to involuntary maltreatment.
- The **International Covenant on Civil and Political Rights, 1966** which India has ratified specifically states 'No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his consent to medical or scientific treatment.'

14. That these international norms have to be adhered to in the

has been held that by the Hon'ble Court that such international commitments /declarations can be read as part of the customary international law as well as part of Article 21 of the Constitution as they relate to protection of life. [vide: PUCL Vs UOI 1997 (3) SCC 433; Vishakha 1997 (6) 241; Kapila Hingorani 2003 (6) SCC 1 & other cases]

15. That at this juncture, the petitioners wish to bring to the notice of this Hon'ble Court, why the clinical trials, of stages I and II, are taking place in India, particularly after the legal change which was seen brought in the patent regime. The entire focus of pharmaceutical industries for conducting stage I and II trials is on the developing/third world countries. There are numerous reasons for pharmaceutical companies conducting drug trials in India and other developing countries. These include logistical and financial reasons, as follows.

15.1. The *logistical reasons* are:

- In the pharmaceutical sector, outsourcing of clinical trials offer the greatest advantage, as the clinical trial is the most labor intensive, time consuming and costly part of the drug development process
- The same drug trials may be cost prohibitive in the pharmaceutical company's country of origin.
- India has a large population that has not been exposed to health-care creating a large pool of 'treatment naïve patients'.

v. Lax regulations relating to drug trials lead to easy approval of trials with little oversight.

15.2. The financial reasons for the conduct of these trials in India are:

- As per U.S industry estimates the cost of drug development has increased from \$318 million in 1987 to \$1.3 billion in 2005 (an increase of 300%) and the time to develop a drug varies from 10-15 years.
- Pharmaceutical multi-national companies had traditionally been hesitant to invest in India because of the lack of patent protection. The strengthened patent protection post-2005 has made India an attractive business destination.

Due to the amendments in the Drugs and Cosmetics Act in 2005 the phase lag has given way to simultaneous multi-country trials. This makes the development of a drug faster and more cost effective and has significantly reduced the drug development time in India.

A true and correct copy 'Profile of US pharmaceutical industry, 2011' indicating the above points is filed as **Annexure P-7 (pages 537 to 557).**

16. That at this stage, the petitioners also wish to submit that pharmaceutical industry is one of the principle engines of the United States economy, contributing \$333 billion (Approx. Rs 16.6 lakh crores) to its GDP and providing direct employment to 6,55,025 people with an average annual salary of \$46,550.

Drug Industry in India is having a size of Rs 1 lakh crores (20 Bn USD) and growing at a rate of 14 % PA, It is the 3rd largest producer of drugs in the world in terms of volume and 13th largest in terms of value. It is a major exporter of medicine exporting about Rs 42000 crores (42%) annually to 200 countries while 65% (68 crores) of Indian population has no access to drugs.

Paper circulated by Department of Industrial Promotion and Policy, Govt. of India, (henceforth, referred to as DIPP) shows a fall in domestic consumption of medicines in 2008-09 by -3%. The growth of new drugs have increased from 1200 in 2005 to 1753 in 2009 and market authorization for vaccine-biotech and medical devices have increased from 10 and 0 to 137 and 936. Indian Patent Office granted 3471 Product Patents in Pharmaceuticals during 2005-06 to 2009-10. Another important development in the Indian industry pointed out by the DIPP is foreign takeover of major Indian drug companies by foreign multinational drug companies. Four major acquisitions of Indian drug companies namely Ranbaxy Labs, Dabur Pharma, Shanta Biotech and Piramal Healthcare. On one hand the industry is now more oriented towards exports and monopoly control and on the other hand it has been promoting trials to earn better profits out of new drugs.

After the passage of the Indian Patent Act and the amendments in the Drug and Cosmetic Act 2005 clinical trials have grown at a great pace in India. As per the Zinnov Management consultant report quoted in SOMO report cited in the later part of this petition (Annexure P-8) that outsourced clinical Trial market will

approx.) in 2005, to 350 million USD (Rs 17500 crores approx.) in 2010. In 2008 clinical trials worth Rs 1345 crores were conducted in India. The Third World Network had estimated that in 2010, 2 million people in India are taking part in Clinical Trial. According to Clinical Trial Registry of India (CTRI) 1574 trials have been registered in India till 15th November, 2010.

17. That under the present dispensation of law and guidelines, following lacunae and shortcomings exist which are resulting in adverse affect on human lives and encroaching on their legal and constitutional rights.

- i. **Injury and Compensation:** No credible, transparent and independent system to determine morbidity and mortality except total reliance on investigators, Ethics Committees and sponsors.

A committee, which is independent of the CRO and sponsor, must be set up to review injury reports and award compensation. There should be no obligation on the participant to make a claim for compensation. This committee must review all adverse event reports and pro-actively award compensation. This is not specifically mentioned in the Schedule Y.

- ii. **Ethics committees (ECs)** must be registered, accredited, and made accountable and liable for their decisions. It needs to be

between scientific and ethical reviews should be made. Independent and outstation Ethics committees about which there is no information beyond incomplete address have to be restricted by law.

- iii. **Conflict of interest:** There is no legal requirement for Investigators or members of the Ethics Committees to declare a conflict of interest. This is a particularly serious problem given the increasing number of hospitals now owned by drug companies and members of ethics committee themselves conducting research. The money, gifts and sponsored foreign trips for investigators should be specifically banned in the Drug and Cosmetic Act
- iv. **Financial Transactions :** There are no regulations for financial payments by companies to CROs, and to Ethics committees, investigators and trial subjects.
- v. **Independent Investigation:** There should be a system in law for intense review of trials that are considered to be higher risk. Complaints of unethical research must be investigated independently and punitive action taken when necessary.
- vi. **Placebo Trials:** In the Drug and Cosmetic Act, there is no provision for specifically disallowing placebo trials specially in serious cases like mental illness, heart diseases, cancer etc when there is treatment available.
- vii. **Post Trial:** The Drug and Cosmetic Act is silent about Post

through trials in India must be made available to the trial population free of cost until they are available in the country, after which time they must be available to everyone at an affordable price.

All the details of drug trials including the patient's contact details must be retained for a minimum period of five years to ensure that they can be traced, followed up and provided compensation or treatment if they suffer injury in the long-term or information about the long-term adverse effects of a drug are discovered.

- viii. **Punishment:** Noncompliance with provisions in the Act of 1940, as amended needs to be made justiciable and punishable. In case of study related injury, disability and death in human participants, the law should hold the sponsor accountable and liable.
- ix. **CROs** must be regulated through registration, accreditation of those who meet standards, and a code of ethical conduct. Violations of this code should be actionable. Trial sponsors as well as CROs will be held accountable for any violations.

18. That the petitioners, as mentioned above, have been working on health issues as well as the issues raised in this petition for quite some time. They have collected information through their own research, documents which are in public domain and also through the RTI. The documents which have been collected by

The broad scenario which emerges from the specific cases of gross violations is that the pharmaceutical companies, in order to capture the market, adopt unethical and even illegal methods and the hospitals/doctors for monetary considerations succumb to such violations and unethical practices, even at the cost of human health and life.

19. That the petitioner is referring to the General and specific cases of violations which have occurred in different states/cities in our country.

General scenario of the illegal clinical trials conducted in India

20. That the highest motivation for pharmaceutical MNC's to come to India is the cost-effectiveness of conducting clinical trials here. India has a high prevalence of poverty and illiteracy, combined with meager healthcare options for the poor. With about 400 million living below the poverty line, 26% illiteracy, and 46% of the population lacking access to affordable healthcare, Indian patients are easy recruitment targets for trials.
- The patient-physician relationship is one of dependence, especially when the patient is poor and illiterate. Physicians often take advantage of their position of authority and conduct clinical trials even when it is not in the best interests of the patient.
 - Furthermore, patients consent to clinical trials because they are often faced with the stark choice between 'some' healthcare and no healthcare. Patients are often ~~unaware~~

~~aware~~ that voluntarily consent for clinical trials is rare, especially in cases of minors and mentally handicapped patients.

- This inevitably leads to the patients being unaware of the hazards of the clinical trials. The trials may involve untested and dangerous drugs, which often have unpleasant, serious or even life-threatening side effects. If these side-effects do occur, the patients are often not compensated. Keeping patients in the dark about these hazards and not providing them insurance cover raises serious legal and ethical issues.
- Despite the law requiring informed consent forms, patients at best provide their thumb impressions on forms written in a language they do not understand, and at worst are not given a form at all. This practice raises serious questions about the 'informed' nature of the consent being given.

The combination of poor and illiterate patients, lack of access to healthcare, exploitative physicians leads to a violation of *patient autonomy* in clinical trials.

21. That in India illegal clinical trials are possible because of lax regulations and their flawed implementation. Some instances of the flawed implementation are:
- The approval of the DCGI must be sought before the conducting of clinical trials. However, instances of the DCGI granting approval for blatantly illegal trials in a matter of days, considering the voluminous nature of protocols which

- Clinical Research Organizations (CRO) are new emerging entities which are actually conducting all the clinical Trials. The Pharmaceutical companies are under pressure to bring more new drugs into the market to be able to be profitable and cut on their drug development budget. Currently, about 50 % of clinical trials are outsourced to CROs. They being powerful stakeholders in the Clinical Trial business, it is a matter of concern that Indian Law does not even acknowledge their existence. There is no legal framework for registration or monitoring of the CROs.
- The ethical-committees are duty bound to safe-guard the rights, safety and well-being of all trial subjects. Inadequate review by these committees and approval of flawed protocols compromises the well-being of the participants. Additionally, doctors who conduct the trials frequently sit on the ethical committees.
- These doctors often receive benefits from the trial sponsors which sometimes becomes the main source of their income, creating a glaring conflict of interest. Doctors conducting trials also receive commissions per patient recruited, creating an incentive to enroll more people in the trials. This leads to a violation of the physician- patient relationship of trust.

A true and correct copy of the joint study conducted by the Centre for Research on Multinational Corporations, Salud Y Farmacos and Centre for Studies in Ethics and Rights in February,

Radar', wherein some of the above aspects have been highlighted is filed as Annexure P-8 (pages ~~55~~ 8 to 66⁹).

22. That the manner in which clinical trials are conducted in our country has been a subject matter of concern in Rajya Sabha. Few excerpts from the debate are quoted below:

Proceedings dated 15.3.2011:

On 15-03-2011, vide Question No 2117 Smt. Kusum Rai, MP asked in the Rajya Sabha following questions:

- a) Number of persons on whom clinical trials have been carried out in the last 3 years, yearwise.
- b) No of persons who died and those who fell seriously ill during these trials, year-wise.

In answer, the Minister of State for Health & Family welfare (Sh. Dinesh Trivedi) said:

- a) & b): " Prior to 17th November, '2008, registration of clinical trials, permission for which was granted between 17th November 2008 to 14th June 2009, applicants were advised to get the trials registered at ICMR registry at www.ctri.in. However, from 15th June 2009, it has been made mandatory to register all clinical trials permission on or after the said date in the Indian Council of Medical (ICMR) registry at their said web site before enrolling first patient in the study.

As per information made available by the National Institute of Medical Statistics (NIMS), ICMR, New Delhi, the

Jan 2007 - Dec, 2007	11
Jan 2008 - Dec, 2008	137
Jan 2009 - Dec 2009	546
Jan 2010 - Dec 2010	806
Jan 2011 - 21 Feb. 2011	122

Deaths during clinical trials occur due to various reasons. Such deaths are investigated for causal relationship by the investigator and the medical monitor of sponsor. The information collected reveal there were 288 deaths in the year 2008, 637 deaths in the year 2009 and 597 upto August 2010.

Proceedings dated 2.8.2011

On 2-08-2011 in response to question no 241 raised in Rajya Sabha by Sh Mohinder Mohan, MP, Shri Gulam Nabi Azad, Minister of Health and Family Welfare, replied that:

"As per information available to the sponsors/CROs, compensation has been paid in 22 cases of trial related deaths which occurred in 2010".

A true and correct copy of Rajya Sabha questions and answers is filed as **Annexure P-9 (Colly)**. (661-683)

23. The Petitioner, itself and through its associates collected information regarding clinical trials through RTI applications. Relevant extracts from the same is quoted below:

Kothari, Indore, the DCGI replied, that Serious Adverse Events may occur during clinical trials due to various reasons. These could be disease related deaths like cancer etc. *The information revealed that there were 132 deaths in 2007, 288 in the year 2008 and 632 in 2009 and 670 in the year 2010.*

b) On **14-10-11** in response to RTI application vide letter no Suchana/CPIO/10-11/04/ 3293 date 11-03-2011, filed by Sh Gautam Kothari, Indore the DCGI supplied the list of clinical trials granted approvals, name of drug, firm name and date of permission. Also collated information as per the following details:-

In 2009, number of Clinical Trials which were granted approval was 488 and list of clinical trials was provided for 108 protocols between 01-10-2009 to 31-12-2009.

In 2010 Number of Clinical Trials which were granted approval was 529

In 2011 up to 30-09-2011 number of Clinical Trials which were granted approval was 189.

A true and correct copy of RTI Questions and answers dated June and October, 2011 is filed as **Annexure P-10 (Colly) (pages**

694 to 719).

SPECIFIC INSTANCES OF ILLEGAL CLINICAL TRIALS

24. That the Petitioners will now deal with specific instances of illegal clinical trials conducted across the country which have violated the fundamental rights of the trial subjects. These trials were

25. The Petitioners submit that rampant clinical trials have been taking place in the State of Madhya Pradesh, the majority of them occurring in Indore. The Petitioners have information/knowledge of the clinical trials taking place in Madhya Pradesh through investigation which was done by the Economic Offence Wing (EOW) of Madhya Pradesh culminating in Report dated 24.06.2011. Further, in view of the fact that the manner in which clinical trials were conducted in the State of Madhya Pradesh, there was a series of questionnaires/debates in the Vidhan Sabha in the Session in July, 2010, November-December 2010, Feb-March 2011 and July 2011. As mentioned above, questions were also raised in Rajya Sabha relating to the clinical trials taking place in the State of Madhya Pradesh. In addition, the information has been collected by the Petitioner through the RTI Applications and the replies. The Petitioner is quoting below the entire Report of Economic Offence Wing and discussing important and relevant facts which emerge from the Vidhan Sabha questionnaire, Rajya Sabha Debates and information through the RTI.
26. That the Report of the Economic Offence Wing to points out the cases of specific violations which have been confirmed by the said Report. This report has been submitted to the Chief Secretary, Govt. of MP, Medical Education Department. For convenience, the entire Report has been quoted below:

Report of the Economic Offence Wing dated 24.06.2011

"The complaint was filed in the Bureau by Dr Anand Singh Raje,

conducted by drug companies on poor patients in attached M.Y. Hospital of M.G.M. Medical College without any supervision.

In the complaint allegations have been made against the following doctors:-

1. Dr Anil Bharani (Prof. Medicine Department)
2. Dr Sali Bhargav (Superintendent, MY Hospital)
3. Dr Ashok Bajpayi (Ex- Superintendent of MGM Medical College)
4. Dr Pushpa Verma (Head of Depart., Ophthalmology Dept., MGM Medical College)
5. Dr Hemant Jain (Paediatrician, Chacha Nehru Bal Chikitsalaya)
6. Dr Apoorva Puranik, Neurologist, MY Hospital.

ALLEGATIONS

- A. Receiving Crores of Rupees from Multi national Drug Companies.
- B. Conducting private trials by Govt. Doctors, while occupying official positions without obtaining consent from the Administration.
- C. Committing fraud on innocent patients and their relatives.

On the prima-facie appraisal of allegations made the Bureau registered a formal complaint vide complaint No- 344/10. Verification of the complaint was done by the Joint DG(HQ), Bhopal. The factual observations that were made by the verifying officer have been presented at Chart A.

1. Indian Medical Council Act, 1956
2. Ethical Guidelines for Biomedical Research on Human Participants, Indian Council Of Medical Research, New Delhi.
3. Code of Medical Ethics Regulation, 2002.
4. MCI Amendment Notification
5. MP Civil Services Conduct Rules, 1965.
6. Prevention of Corruption Act, 1988
7. Drugs And Cosmetic Act

SIGNIFICANT POINTS FOUND DURING INVESTIGATION: The following irregularities and shortcomings have been found:

1. The Principal Investigators (PIO) were themselves the members or member secretaries in the Ethical Committees and these committees did not follow the standard practices and ethical guidelines fully.
2. The Principal Investigators also violated the Ethical Guidelines repeatedly.
3. The Principal Investigator and the Ethical Committee did not take appropriate steps as was expected from them in cases of Serious Adverse Effects (SAE).
4. CROs(Contract Research Organization), Ethical Committee and PIO did not follow the established principles of safeguarding the interest of the patients.
5. The core principles of informed consent were disregarded.
6. On several instances the Principal Investigator contravened the Section 20 A (Professional Conduct) of the Indian

7. By accepting money for themselves and by undertaking sponsored foreign trips the Principal Investigator clearly contravened the "conflict of interest" doctrine.
8. The trials did not in any way follow the established rules which would have ensured profits to the institutions where they were carried out. The institutions did not gain in particular from the trials carried out by the PIOs.
9. The patients on whom the drug trials were carried out deposed that no transparency was displayed while carrying out trials and they were even denied entitlements that were due to them.
10. In instances of Serious Adverse Effects the dictum of financial safeguard or insurance was contravened.

RECOMMENDATIONS: On verification of the complaint the majority allegations have been found to be amounting to be contraventions. However, sufficient basis was not found to initiate criminal action. On the basis of the evidences found it is proposed the following actions at the level of Govt. should be taken:

1. For not safeguarding the interest of the patients as per the established principles by the CROs, Ethical Committees and PIOs, for not conforming to the laid out guidelines by the institutions where the trials were carried out, for contravening the financial safeguards/insurance dictates actions should be taken as per law under the Sections 20 A and 24A as per Annexure-1 by the State Medical Council against the Principal Investigators and members of the

2. For disregarding the core principles of informed consent, for not maintaining transparency and for denying the trial subjects of their due entitlements, and for violating the principals of 'Ethical Guidelines for Biomedical Research on Human Participants' (Annexure-2) of the ICMR, the Indian Council of Medical Research (ICMR) should contemplate taking appropriate action against the Principal Investigators, Ethical Committees and CROs.
3. Action could be contemplated under the conduct rules of State Medical Education department of Govt. of MP as the trials did not in any way follow the established rules which would have ensured profits to the institutions where they were carried out. The institutions did not gain in particular from the trials carried out by the PIOs. (Annexure-3).
4. The Govt. should consider taking action by following up with the MCI against the principle Investigators for accepting money for themselves and by undertaking sponsored foreign trips under code of medical ethics regulation 2002 and amendment notification dated 10 December, 2009 of MCI.(Annexure 4)
5. Out of the money received from clinical trials 10% was to be deposited in the Medical Education Department account as per the letter dated 3.10.08 (Annexure 5) of Mahatma Gandhi Memorial Medical College, Indore, which still under consideration and which has still not been deposited.

The report of the Bureau with the recommendations is submitted

True and correct copy of Report Dated 24.6.2011 of the 'Economic Offences Wing, Madhya Pradesh', is filed as **Annexure P-11 (pages 720 to 746)**.

TABLE IN THE EQW REPORT

Names Of Doctors	Number of Protocol	No. Of Pts (Who Have Been Subjected To Drug Trial)	Approx. Money Received (2006-2010)	Death/S erious adverse effect s	Patient's Consent (Right/ Wrong)	Site Of Trial
Dr. Anil Bharani	15	400	1,53,00,000	30	Wrong	M.Y. Hospital Indore
Dr. Hemant Jain	25	2500	1,70,00,000	18	Chacha Nehru Children Hospital Indore
Dr. Shalil Bhargav	20	300	1,05,00,000	18	M.Y Hospital & Gyan Pushp Research Centre Indore
Dr. Apoorva Pauranik	7	40	26,00,000	8	Wrong	M.Y. Hospital Indore
Dr. Ashok Bajpayee	5	35	48,00,000	7	Wrong	M.Y. Hospital Indore
Dr. Pushpa Verma	1	32	8,00,000	Wrong	M.Y. Hospital, Indore
Total	73	3307	5,10,00,000	81		

27. That not only in the above Report but also in the Vidhan Sabha questionnaire/debates, several important aspects of clinical trials were discussed. Important excerpts (translated from Hindi) from

July 2010

The debates took place on 23.7.2010 and 30.7.2010. Questions were put by the MLAs regarding drug trials in Indore, irregularities in obtaining consent of trial subjects, sum of money paid to investigating Doctors and the Principal Investigators being Members of Ethics Committee which approved and monitored the Trials. It was pointed out that in the last 5 years, drugs have been tested on 1170 children and 1521 patients for which 6 doctors were paid Rs. 2.00 Crores by the drug companies. It was also informed by the MLAs that the foreign Companies have developed their own format regarding consent which in English having 6-7 pages. The speaker had put a specific question:

Speaker: "A question is being repeatedly asked on how many patients drug trial is conducted."

Mahendra Hardia, State Minister for Medical Education answered:

"Speaker sir, the persons who suffered adverse effect is 51, total number of patients is 2365 out of which 1644 are adults and 721 children."

November-December 2010

On 23 November 2010 vide question no 544, Hon'ble MLA Sh Paras Saklecha sought details of trials conducted on children:

Dangerous drug trials on children and girls

Mr.Paras sakhlecha -

"Can Chief Minister Mr. Shivraj Singh Chauhan please tell

- Chemical drug trial/ vaccine trials are conducted on how many children in the state? Make available information regarding the names of the doctors who conducted the trials and also the names, addresses, and fathers name of the children on whom the trials were carried.
- How many trials from trial mentioned in question 'a' have been approved by the World Health Organization & which of these trials have been approved by multinational companies and for these trials what amount was paid to which doctor in which year? Give details?
- On how many girls / young females was the trial of V-503 (multivalent HPV vaccine) cervical cancer and vaginal cancer, done in last 5 years? And who had done this trial, name the doctor? In this particular trial from which cancer specialist, immunologist & gynecologist and obstetrician's opinion was obtained? Name the females on whom this trial was conducted along with their addresses and age? Provide the list too?
- Whether it is true that after 5-7 years following all doses of multivalent HPV vaccine the capacity to fight against HPV i.e. the antibody titer will be completely lost for this virus while cervical cancer is generally occurs during age of 40-45 yrs? Then why the vaccine trial is done on females of 15-25 years of age? Give reason?

Chief Minister (Sh. Shivraj Singh Chauhan),

- Drug trial was carried out on 3 children and vaccine trial on 866 children for during the time period mentioned in the question 'a'. This trial has been carried out by Dr. Hemant Jain, Professor Department of Paediatrics, Medical college Indore.
- According to the information collected from relevant doctors as per question none of the trial were sponsored by WHO. Given below are the details of the trial and against them are mentioned the names of Multi-National Companies which sponsored these trials :

	Description of the trial	Name of the Multi-National Companies
1	Pantavalent vaccine	L.G Life sciences
2	Laboprogel	Johnson & Johnson
3	Pantavalent vaccine	L.G life sciences
4	Meningococcal A.C.W.Y vaccine	Glaxo Smith Cline
5	HPV Vaccine	M.S.D
6	Hepatitis A vaccine	Crusei
7	H1N1 vaccine	Panacea

Those mentioned from S.No. 1-6 are conducted by Dr. Hemant Jain Professor, Department of Pediatrics Medical College, Indore. He got the amount of 1, 49,650/- in Year 2009 from L.G life sciences (South Korea). Trial mentioned under S.No. 7 was conducted by Dr. Anil Gauri Associate Professor

which he got amount of Rs. 70,217/- from Panacea Company(New Delhi) in year 2010.

- Vaccine trial as per the question in the last 5 years was carried out only in 2010 on 44 children and young women. In this particular trial, Dr. Hemant Jain, Professor, Department of Pediatrics Medical College, Indore was the Principal Investigator. No Immunologist was involved & guidance from Dr. Mukta Jain was obtained who is a gynecologist and obstetrician. Drug trial was not done on any female child therefore, rest of the questions did not arise.
- After taking all doses of vaccine as mentioned in question, immunity will last till after 7 years due to which infection from HPV virus is prevented, as the action of the vaccine is to prevent and not treat the infection of the virus. Cervical cancer and Vaginal cancer occurs 20 years after the infection of the virus, that is why it is appropriate to use the HPV vaccine in the age group 9-26 years.

Several questions were raised regarding the manner in which clinical trials are conducted, vaccine trials having dangerous side effects and such chemical combinations are used which are causes of dangerous diseases. The answer given by the Hon'ble Minister was that a Committee has been constituted and that Committee has recommended ban on new trials while allowing pending trials to continue.

On 10 and 17th March 2011 discussion has taken on the question of drug trials and whether the clinical drug trials are conducted in Private Hospitals / Research Centres. On 31st March 2011 specific questions were put with regard to drug trials on psychiatric patients

On 31st March 2011 vide question no 5626 the Hon'ble Member Sh. Paras Saklecha asked

DRUG TRIALS ON PSYCHIATRIC PATIENTS

Mr.Paras Saklecha – "Would Mr. Chief Minister please,

- Provide information regarding drug and vaccine trials done by Professors of Medical College and doctors of Govt. Hospital in their private clinics and details of Ethical Committee which gave permission?
- Have the various psychiatrists, namely, Assistant Superintendent of MY Hospital, Dr. V S Pal, Superintendent of Mental Hospital, Dr Ramgulum Razdan , Assistant Professors of Mental Hospital Dr. Ujjwal Sardesai, Dr Pall Rastoge, Dr.Abhay Paliwal, conducted drug trails on 2000 mental patients in their own personal clinics? Give details?
- Was Dr. Salil Bhargava from MY Hospital also conducted trial in "Gyanpushpa Research Center" clinic? Give details?
- What are the registration numbers of these clinics according to Section 3 of the M.P. Clinical Establishment and Registration Act 1973?

- Did these doctors inform the health department about these trials under Sections 4 and 5 and if not what action has been taken against them under Section 8?

Chief Minister (Mr. Shivraj Singh Chauhan) –we are gathering information for question a to d

"The doctors of Indore Medical College conducted drug/vaccine trials in the private clinics as detailed in Annexure A, and only one doctor of Dr Mukta Jain, gynecologist of Govt. run Prakash Chand Sethi Hospital was involved in vaccine trial under Dr Hemant Jain, her husband for which was given show cause notice".

The details asked in question b, is placed at Annexure B, details of Dr Salil Bhargav and other doctors in Questions c and d are in Annexure C and D respectively.

On 31st March 2011 vide question no 6790 the Hon'ble Member Sh. Paras Saklecha asked re:

Drug trial of Tadalafil (drug used for sexual dysfunction) on patients of hypertension

Mr.Paras Saklecha – "Can Mr. Chief Minister please tell us that?"

- Is it true that Dr. Anil Bharani & Dr.Ashish Patel from Mahatma Gandhi Memorial Medical College have conducted Phase -3 trials of Tadalafil (drug used for Sexual Dysfunction) on patients of Pulmonary Artery Hypertension

Please provide documents related to this trial including Phase-1, Phase-2, & animal toxicity report?

- Regarding the drug trials of above mentioned drug provide us the meeting minutes of official ethical committee as per the Schedule 'Y' of Drug and Cosmetic Act 1945, permission letter from DCGI, & information related to publication of this research?

Name and addresses of the trial subjects, & clinical trial insurance policy must be made available to us?
- Is it true that M.G.M.Medical college Indore is shown as a sponsor company for drug trials mentioned in part 'a' above in drug trial related CTRI registration? If yes then avail us the documents & information related to permission from Dean of the College & Medical Education Department?
- Does the M.P Drug Controller have the information that to which company this license has been given by DCGI / CDCSO on 14th November 2009 for commercial production and sell of Tadalafil drug?

Chief Minister (Mr. Shivraj Singh Chauhan) -- collecting information from 'a' to 'd'

- Professors and Head of the department, department of medicine have been doing an experiment of Tadalafil drug which is a PDE-5 inhibitor drug since 2005 on patients of pulmonary hypertension. This project based on Tadalafil

- The drug research mentioned in question 'a' is a faculty pilot project so does not require the permission from DCGI, New Delhi according to rules for the conduct of this project. Approval from ethics committee was essential so it does have that. Permission letter from organizational ethics committee has been kept in library in annexure -1 & minutes of ethics committee is also kept in annexure 'a' in library. The research work mentioned in question 'a' is not complete so it is not published yet and the patients involved in this pilot project as mentioned above are following with the information of their age and sex. Patients involved in trial of Tadalafil drug are the following

Name of the patient	Age	Sex
Mr. Prem Kishore Patidar	35	Male
Mrs. Arti Sharma	35	Female
Mrs. Gyanvati Bai	31	Female
Mr. Mohammad Aashiq	17	Male
Miss. Rupali Rawat	24	Female
Mrs. Uma Devi Sutar	40	Female
Mrs. Rajkumari Bai	35	Female
Mrs. Raziya Sultana	46	female
Mrs. Bahgirathji Bai	70	Female

The addresses of the patients should not be provided according to medical ethics. Institution has not obtained any financial aid from any organization therefore it was not

- c. This pilot project has been registered on the website of clinical trials of registry of India officially because this work is being carried in the same college without any external sponsorship or aid. Without any sponsorship available facilities are used for the project but it is wrong that the institution has been named as a sponsor company and that no permission was obtained from the Dean of medical department.
- d. According to the information published on website of DCGI New Delhi this drug Tadalafil is a drug verified as a new drug as on 11-9-2003 for Erectile Dysfunction. On 14-11-2009, it is also verified as Tadalafil 20mg tablet has a extra indication for the treatment of Pulmonary Arterial Hypertension (PAH). Company's name is not available on the website therefore, the relevant information is not within the knowledge of the Controller of Food, and Drug Administration."

July 2011

On 12th July, 2011 and 19th July 2011, questions were put with regard to clinical trials on children and generally drug trials in the Indore town and in Indore region. Shri Narottam Mishra, Parliamentary Affairs Minister stated that total 5 deaths occurred due to drug trials as per available information and that no compensation has been awarded to the deceased.

November 2011

True and Correct copies of the Vidhan Sabha debates, questions and answers are filed as Annexure P-12 (Colly) (pages 812 to 812).

28. The petitioner is referring to the debates in Rajya Sabha which took place in relation to the State of Madhya Pradesh, as follows:

Rajya Sabha; Question No.1046; Answered On 09.08.2011
Illegal Clinical Trials of Drugs

1046 SHRI MAHENDRA MOHAN

Will the Minister of Health And Family Welfare be pleased to state:

- (a) Whether Government is aware that some companies are carrying out illegal clinical trials of medicines on poor people in various parts of the country?
- (b) If so, the details thereof and what action has been taken against them.

ANSWER

THE MINISTER OF HEALTH & FAMILY WELFARE
(SHRI GHULAM NABI AZAD)

(a) to (c):

"As regards the allegations of clinical trials conducted in MGM Medical College, Indore, investigations are being conducted to assess whether there are any discrepancies under the Drugs and Cosmetics Rules in conduct of these clinical trials".

29. That Minister of Health and Family Welfare gave statement in Rajya Sabha on 20th December, 2011 with regard to Regulation of

2008 onwards was enclosed. The details given therein show that gross illegalities and unethical practice were done while conducting clinical trials. But the action taken was only to issue warning or correcting the procedure except in one case pertaining to 'tadalafil trial' that two doctors were stopped from conducting clinical trials for a period of 6 months. Out of these two doctors, Dr Anil Bharani is also the Secretary of Ethics Committee, M. Y. Hospital. The Minister acknowledged that there are loop-holes and weaknesses in the legal regime and therefore, referred to the draft notification dated 18.11.2011. A true and correct copy of the Rajya Sabha questions and answers dated 20th December, 2011 is Annexure P- 13 (pages 813 to 816). This news has also appeared in the Indian Express dated 2nd January, 2012 and in The Hindu dated 5.1.2012, true and correct copies of the same are Annexure P-14 (Colly) (pages 817 to 818).

30. That the Petitioner is giving summary of different complaints which were filed before the National Human Rights Commission, Lok Ayukta M.P., Ministry of Health and Family Welfare and Chief Secretary. The complaints show that the attention of authorities has been repeatedly drawn to the violations committed due to clinical trials.

Summary of the complaints filed with various Authorities :

- I. On 10-01-2011, complaint was made to the National Human Rights Commission by Dr Anand Rai in which it was alleged that there was flagrant violation of human rights of the mentally ill by

was taken. He annexed a list of 11 protocols relating to drug trials on mentally ill and mentally retarded patients on which drug trials were carried out.

- II On 2nd July 2011, complaint was made to the Chief Minister of MP with copy to state health minister and important state officials, pointing the details of EOW report urging them to initiate action against the doctors and ban clinical trials in Indore.
- III On 1st September complaint was filed by Swasthya Adhikar Manch with the Prime Minister of India, New Delhi. In the complaint the details of illegal nature of trials was given enclosing the EOW reports and the PM was urged to get an independent inquiry conducted as the MP Govt. is insensitive towards the issue and has expressed that the action in the case was beyond their preview. However, the PM forwarded the complaint to the Chief Secretary, Govt. of MP for action on 13-09-2011.
- IV On 19-09-2011, complaint was made to the NHRC by Swasthya Adhikar Manch in which the manner of violation of Human Rights of trial subjects by the doctors was pointed out specifically highlighting conflict of interest of doctors and violations of principles enunciated in the ICMR code 2006, urging to carryout investigation of the issue, compensate the patients who have suffered serious Adverse Effects and take action against members of Ethics Committee and others.
- V On 19-09-2011, in a joint complaint filed by Dr Anand Rai and Sh Veejay Chaudhary before the Chief Secretary, Govt. of MP, they

College Indore and Dr Pankaj Aggarwal at Govt. Indira Gandhi Medical College, Shimla. In 2007, the research, was published by the above doctors in Indian Heart Journal. On the basis of this research Cipla Pharmaceutical Company, Mumbai had obtained manufacturing rights for commercial production of Tadalafil for use on patients of Pulmonary Arterial Hypertension from the Drug Controller General of India and now ready to bring this medicine in the market as Pulmopres (Tadalafil) 20mg tablet. The trial was registered with Clinical Trial Register of India vide CTRI/2009/091/00074 by Dr Anil Bharani. As per law since the sponsor of the above trials were MGM Medical College, Indore therefore, the rightful owner of these rights vests with the Govts of M.P. and H.P. But with conspiracy of Dr Anil Bharani and Cipla Pharmaceutical Company, Mumbai with the DCGI, New Delhi a loss of Rs 500 crores has been caused to Govts. Of M.P. and H.P.

In the complaint, it was stated that in the USA, the manufacturing rights of the medicine were sold by Eli-Lilly Pharmaceutical company to United Therapeutics Company for USD 150 million (Rs 500 crores) and the estimated valuation of this transaction in India would work out to around the same amount. And since officials of Central and State Govts. are involved in this transaction an enquiry by CBI (Anti Corruption Wing) should be done.

- VI Individual Complaints: Complaints were filed by four individuals who suffered Serious Adverse Effects (SAE) as a result of Drug Trials.

illness due to trials carried out in MY Hospital, Indore for his heart ailment for which he had no knowledge.

On 26-12-2011 Sh Krishan Gehlot made a complaint before the NHRC alleging that clinical trials for respiratory disorders was done on him and as a result he became bed ridden and his respiratory problem has become worst and that he was not informed about the trial.

A complaint was filed Ajay Naik with the Sanyogitaganj Police Station, Indore on 01-11-2010 wherein he has pointed out trial on his 2 day child without consent, referred in later part of this petition.

A complaint dated 2-10-2010 was filed by Sharad Geete husband of Sheela Geete to the State Health and Medical Education Minister, alleging death of his wife due to drug trials done without informed consent.

The petitioner gave complaints about illegal and unethical drug trials to the Prime Minister, Chief Minister of MP, Drug Controller General of India, NHRC among others. The petitioners are not enclosing all the complaints except complaints dated 10-1-2011, 01-09-2011 and 19-09-2011 (two).

True and correct copy of the complaints dated 10.1.2011, 19.9.2011, etc made before various authorities is filed as **Annexure P- 15 (Coliv)** (pages 82 to 83).

31. That the issue of clinical trials, the violations committed therein of the

Article 21 of the Constitution was raised in several Newspaper, journals and Magazines.

Summary of important news items, articles in newspaper, journals and magazines:

- I. Dr. Vikram Patel, Psychiatrist had pointed out in an article titled "Ethics of Placebo" published in the Indian Journal of Medical Ethics (IJME), the ethical issue of trials on severely ill mania cases of a Placebo. The trial was unethical as it was carried out on 290 patients of acute mania in 8 health facilities in India by withdrawing the treatment. It was sponsored by Johnson and Johnson of USA.
- II. On 16 June 2010 news appeared in Hindustan Times titled, "Gas Victim or Guinea Pigs" reports drug trials conducted on 165 gas victims and published statements of various patients who had undergone trials but were not even aware at the time of trials that they were being tested for drugs.
- III. On 20 January 2011, news appeared in Free Press, Indore ed., titled "Sex drug also tested upon mentally challenged", wherein two senior government doctors tried sex drugs on mentally challenged patients. The drug was tested on 172 mentally challenged in 24 sites in India. According to the news the drug has not been permitted in USA for Premature ejaculation(PE).
- IV. In May 2011 issue of MIMS editorial by editor Dr C.M. Gulathi titled "Clinical Trials: A Matter of Life and Death" mentioned

conducting Trials, violations of GCP and ICMR guidelines and approvals of trials by non-verifiable Ethics Committees.

- V. Article published in the week title, "The bane of Cure", Jan 23, 2010 by Jisha Krishanan pointed out case histories of two women one of Mumbai & other of Rajasthan suffering from multiple sclerosis and rheumatoid Arthritis who underwent trials without their knowledge. She focused on issue of trial drugs being mostly life style drugs but trial subjects were from the lower economic strata as it was nothing more than money-making business.
- VI. On 8 May 2011 news item appeared in Patrika titled ".... Then the companies would have been locked up" reports on the workshop in Indore on drug trial addressed by Dr CM Gulati where he raised questions like out of 179 ethics committees in the country 40 only were genuine, the trial protocols submitted for approval of DCGI run into hundreds of pages but are approved within a week, the law on drug trial may be stringent but nobody follows it.
- VII. Down to earth, June 16th -30th, 2011 published article by Ankur Paliwal titled, "Ethics on Trial" commented on the extent of business. Clinical trial generated business worth 1345 crores in 2008 and value of all Global trials was worth Rs 1,56,870 crores. It pointed out that 3rd Phase trial were most expensive and doctors receive amounts varying from Rs. 35000 – Rs. 100000 per patient recruited which became the dominant source of Income for these doctors. Most of Multi-National companies like Eli Lilly,

- VIII. On 10 July 2011, article titled, "Experiments with untruth by Rema Nagarajan" appeared in Times of India. The article discusses that the Ethics Committees meant to protect the rights of patients were doing roaring business especially the Independent Ethics Committees (IEC). One of the ethics committee, Biomedical Ethics Committee in Delhi has quoted its rates of approval on its website referred to as "Ethics Review fees". It points out that an Ahmedabad based Veeda Clinical Research Ltd which is a CRO runs Independent Ethics Committee. Anybody who can put together a bunch of seven people fitting the rather loose description can run an IEC and charge to clear trials.
- IX. On 2 January 2012, Washington Post published article, "India's Drug trials fuel consent controversy" discusses the no of deaths due to participation in trials, and that trials has saved companies 40% cost. It also highlights that US companies like Pfizer has taken a decision to cancel trials in Indore.
- X. On 2nd January 2012 in Indian Express points out that a paltry Rs 5000 fine was slapped on guilty doctors after inquiry by to member probe committee set up by Chief Medical and Health officer, Indore. The committee advised that criminal proceeding should be started against them and their practicing licences should be cancelled

The petitioner is enclosing true and correct copies of the Newspaper reports in Patrika (Hindi) dated 8-05-2011 and Indian Express 2-1-2012, articles in the journals Indian Journal of Medical Ethics, Issue Jan -March

23rd January 2011, Down To Earth June 16-30, 2011, Washington Post 2-01-2012 as Annexure P-16 (Colly) (pages 84 to 87).

32. That with the above general back-ground and specific violations in the State of Madhya Pradesh, the petitioner craves leave to discuss the violations which have occurred in Indore, in different hospitals which are under Mahatma Gandhi Memorial (MGM) Medical College, Indore and other trial which have been conducted by the doctors employed in these hospitals, privately.

TRIALS IN INDORE:

33. Indore has gradually emerged as an important centre for clinical trials after the year 2005. MGM Medical College, Indore with its attached Maharaja Yashwantrao (MY) Hospital, Chacha Nehru Bal Chikitsalaya Hospital, Mental Hospital and Psychiatric Hospital became a major centre for drug trials. Large number of renowned private hospitals such as Choitram Hospital, CHL Apollo Hospital, Charak Hospital, Total Hospital, and Greater Kailash Hospital also took part in number of trials.

Trials in Mahatma Gandhi Memorial (MGM) Medical College, Indore and Hospitals attached to it: Maharaja Yashwantrao (MY) hospital, Chacha Nehru Bal Chikitsalaya Hospital, Mental Hospital

34. That since 2005, large number of illegal and unethical clinical trials were carried out by doctors of the MY Hospital. The doctors conducting the trials got huge personal benefits in the form of money, sponsorship for foreign trips and gifts. They not only violated the service Conduct Rules under which they were employed by the Govt. and rules of Professional

compromised the interest of the patients by making them trial subjects. The violations have been discussed under following heads:

Financial Benefit

- 34.1 In the EOW report obtained under the RTI, it has been reported that from 2006-10, 76 clinical trials were performed by 6 doctors of MY hospital. These trials involved 3307 subjects including 1833 children, out of which 81 suffered serious adverse effects including deaths. The doctors involved took a total remuneration of Rs 5.10 Crores for conducting these trials. Doctors involved in these trials used the facilities of the government-funded M.Y. Hospital and Chacha Nehru Hospital, Indore (both affiliated with M. G. M. Medical College) for purely personal benefits. This amounts to a misuse of their position and power. The money earned was deposited in the personal accounts of the doctors without the permission of the institutions, violating the State Government Service Rules.
- 34.2 The Economic Offences Wing (EOW) in its Report, which is quoted above, released the following data:
- Dr. Anil Bharani used 400 patients in 15 trials, made Rs. 1.53 crores.
 - Dr. Hemant Jain used 2,500 patients in 25 trials, made Rs. 1.70 crores.
 - Dr. Salil Bhargava used 300 patients in 20 trials, made Rs. 1.05 crores.
 - Dr. Apoorva Pauranik used 40 patients in 7 trials, made Rs.

- Dr. Ashok Bajpai enrolled 35 patients in 5 trials, made Rs. 48 lacs.
- Dr. Pushpa Varma enrolled 32 patients in 1 trial, made Rs. 8 lacs.

- 34.3 As per information provided by Public Relation Officer, MGM Medical College, Indore under RTI, the following doctors had made foreign trips by accepting sponsorship of the companies for which they were conducting trials

- Dr. Salil Bhargav, HOD Medicine undertook trips to Spain for 4 days (Conference); London for 7 days (conference) and Hong Kong ;
- Dr. Apoorva Pauranik travelled to USA for 11 days (Conference);
- Dr. Hemant Jain travelled to Europe for 6 days (Attending meeting);
- Dr. Ashok Vajpayee undertook two trips to USA one in 2007 for 29 days and second in 2009 for 30 days (Holiday trip);
- Dr. Pushpa Varma, Hongkong for 5 days (Conference);
- Dr. Anil Bharani made 5 trips to USA for total duration of 73 days (Conference and holiday).

The above facts establish that there is a direct conflict of interest at play between patient welfare and financial gains. This information raises serious legal and ethical concerns.

34.4 The EOW report points out serious violations in procedures by the doctors and the Ethics Committee while carrying out these trials. There were findings of various types of gifts being given to these doctors, in violation of the Medical Council of India Guidelines. By accepting money, gifts and sponsorship from drug companies these doctors become liable for action under the MCI guidelines.

34.5 In the EOW report, the DG, EOW has found the following violations:

1. "The principal investigator was also the member and member secretary of the Ethical Committee, and they did not follow the standard practices and ethical guidelines".
2. "The Principal Investigator (PIOs) and Ethical Committee did not carryout the necessary steps in cases of serious adverse effects".
3. "CROs(Contract Research Organization), Ethical Committee and PIO did not follow the established principles of safeguarding the interest of the patients"
4. "The core principles of informed consent were disregarded".
5. By accepting money for themselves and by undertaking sponsored foreign trips the Principal Investigator clearly contravened the "conflict of interest" doctrine.

EOW further recommended initiating action against the members of the ethical committees and all the Principal Investigators under

Violation of Informed Consent

35. The doctors who conducted the trials did not follow the due process of obtaining informed consent of patients.
- 35.1 The consent forms and information sheets which the Petitioners have collected through RTI show violation of the Drugs and Cosmetics Rules, as well as all national and international ethical and GCP guidelines. The sample format which was used did not contain essential elements for obtaining consent. It merely stated that the subject had read and understood the information letter, but information letter was not provided or signed. Further, the risks involved in these trials were not explained. The patients who were subjected to these trials trusted their doctors and were under the impression that they were receiving treatment for their illness. The patients were neither told about the purpose and procedure of drug trials nor were the possible adverse effects explained to them. There was a total failure in obtaining Informed Consent from these patients for participation in the drug trials. The RTI information relating to ethics committee reveals that verbal consents were also taken. True and correct copy of the sample consent form is marked as **Annexure P-17 (pages 898 to 901)**.
- 36.2 The EOW during the investigation examined the consent forms and also video recorded statements of large number of patients which is available with them and on this basis it concluded that, "The core principles of informed consent were disregarded" in their findings and recommended actions by ICMR against these

36.3 On perusal of the Vidhan Sabha debates and questions, it is seen that the violation of proper consent of patient was repeatedly raised.

36.4 As would be discussed in later paragraphs large number of trials were carried out on children, adolescent and mentally ill patients for which proxy consents were taken. The International and national laws have given detailed guidelines for obtaining consents, which were violated here.

Adverse effects of the Clinical trial

37. These are common occurrences in the conduct of trials which include disability, prolonged admission in hospital or death of the trial subject but these are generally not disclosed.
- 37.1 In the EOW report it has been reported that in the 73 protocols relating to which trials were carried out, 81 persons suffered Death/Serious Adverse Effects which included 18 children. These were not disclosed to the Ethics Committee nor were any compensation paid to the victims.
- 37.2 On the basis of information collected under RTI, it has been found that 5 deaths of trial subjects have occurred in CHL Apollo hospital but no mechanism for carrying out independent investigation to determine the cause of death existed and they were generally ascribed to causes unrelated to drug trial like progress of disease or natural causes.
- 37.3 In the question raised in MP Vidhan Sabha (referred to above) the issue of death of Sheela Geete of Khandwa was discussed, and

clinical and vaccine trials. However, the Govt. continued to deny that any death has occurred as a result of drug trial. Even though large number of deaths occurred during trial but due to lack of establishment of causal relation between trial and death the death, is never reported as death due to drug trial. Even in cases of *placebo trials* done on patients suffering from diabetes, heart diseases, cancer and patients of psychiatric illness serious adverse effects have resulted due to withdrawal of normal treatment.

No compensation to trial related injuries and deaths

38. That another related issue is that no compensation or insurance cover was given to cases of trial-related injury or deaths, as none of the deaths were attributed to participation in drug trials. The involved doctors concealed all information on the causes of such deaths.
- 38.1 Information collected under RTI has revealed that the insurance policies are also faulty. Some of the insurance policies executed at the drug trial reveal the following shortcomings:
- i) The insured person is the sponsor company and not the individual subject. In the Policy, the insured persons are Daiichi Sankyo Pharma Development, New Jersey, USA; Boehringer Ingelheim, Korea, Eli Lilly Company (India) Pvt. Ltd. The insurance is done to protect the interest of the sponsor company against liability arising due to trials.
 - ii) The period of insurance is generally one year and claim has to be made within 30 days of expiry of insurance on the company

iii) The insurance policy is worded in a manner that compensation would be paid only on the injury being caused by trial drug or directly attributed to participation in the trial. A linkage has to be established between the trial and injury and the responsibility has been given to PIO and EC which are interested persons as a result till date not a single injury has been linked to drug trial.

True and correct copy of the sample Insurance policies/cover notes are placed as Annexure P-18(Colly) (pages 902 to 933).

Violation re: Ethics Committee

39. The law and guidelines entails large responsibility on the Ethics Committee but in Indore it has been seen that the Principal Investigators (PIOs) are also members of these institutional committees. Many trials have been approved by outstation committees which have been designated as Independent Ethics Committees (IECs) in the Rules of 1945 as amended with non-verifiable addresses having remote chances of monitoring. The Institutional Committees and IECs do not exercise any monitoring of trials and do not have any information regarding the adverse effects.
- 39.1 The Ethics Committee in MGM Medical College, Indore has 27 members but the approvals for trials were given when only 5 members were present. Many of the doctors who were principal investigators were members of Ethical Committee that approved the trial. Dr Anil Bharani (Cardiologist) was the C

1,53,091,000/-. These trials were conducted in MY Hospital and resulted in deaths of 30 patients as per the EOW Report referred to above. Similarly, Dr Ashok Bajpai, Prof Pushpa Verma (Eye Dept.) and Prof Salil Bhargav who were Principal Investigators were also members of the Ethics and Scientific Review Committee. They work on principles of mutuality, approving each others' trials.

- 39.2 The doctors who conducted trials in their private clinics took approval of the Independent Ethical Committees (IECs) located in far-off towns instead of taking approval from committees of their own towns or institutions where they were employed. There was no transparency in obtaining these approvals and no monitoring of trials by these outstation independent committees (IECs). It has been reported that certain trials were conducted in Delhi where a fee was being charged for approval for conducting trial referred to in the *"Ethics Review Fee" (ref: Ethics of untruth by Rama Nagrajan, TOI, July,10,2011)*. True and correct copy of the article: *'Ethics of Untruth by Rama Nagrajan, TOI, July,10, 2011'* is has already referred in Annexure P-17.
- 39.3 Trials where approvals were taken from Independent Ethics Committees, were conducted by Dr Salil Bhargav, Dr Ramgopal Razdan, Dr. VS Pal, Dr Ujjwal Sardesai, Dr Abhay Paliwal, Dr Pall Rastogi, Dr Atul Shinde, and Dr Rajesh Bharani (all of whom were employed with MGM Medical College) and conducted trials in private clinics. They did not seek approval of the Ethics Committee of the institutions where they worked but obtained

This was done despite institutional ethics committees being available in MY Hospital, Indore:

- Dr Salil Bhargav obtained approval of Independent Ethics Committee of a private hospital, namely, Total Hospital Ethical Committee, Indore for 11 protocols and from Ethics Committee located in Bangalore for 1 protocol. He conducted research in his private clinic. He was Medical Superintendent of MY Hospital, while he conducted trials in his private hospital.
- Dr Ramgopal Razdan, is the Head Of Department, Psychiatry, in MGM Medical college and the Director of Government Mental Hospital. But he obtained approval for conducting trials from ADITYA ETHICAL COMMITTEE located in Ahmedabad. Trials were conducted in his private clinic at Indore.
- Dr VS Pal (Psychiatrist) was heading the Department of Psychiatry and Deputy Superintendent of MY Hospital. He obtained approval for a drug trial conducted in his private clinic from CHL Apollo Hospital, Indore.
- Dr Ujjawal Sardesai, Psychiatrist, obtained approval from committee located in Poona for trials conducted on psychiatric patients in his private hospital Sanvedna, Indore.
- Dr Pall Rastogi conducted trials in Suyash Hospital, Indore and Great & Happy Care, Indore but the approval was

- Dr Abhay Paliwal, obtained permission for trials conducted in Indore from an IEC located in Pune.

Tadalafil Trials

- 40 That in addition to the above, in MY hospital Indore, the trial of a new drug 'Tadalafil' was conducted by committing several violations.
- 40.1 Rule 122DA(1) of the Drugs and Cosmetics Rule, 1945 clearly states that:
- 'no clinical trial for a new drug ... for any clinical experiment by any institution shall be conducted, except under and in accordance with permission in writing of the Licensing Authority/ (DCGI in this case).*
- The form and manner of permission is clearly defined in the said Rule. Further 122E(b) defines what a *new drug* means:
- 'a drug already approved and now marketed with modified or new claim namely, indication, dosage, dosage form and route of administration'*
- 40.2 Dr Anil Bharani and Dr Ashok Patel conducted phase III trial for the drug named 'Tadalafil' without permission, in clear violation of the rules. This Drug has been approved for marketing for 'Erectile Dysfunction' in male patients. 'Erectile Dysfunction' is defined as:
- 'Male impotence, and sexual dysfunction characterized by the inability to develop or maintain an erection of penis during sexual*

The Tadalafil drug was administered to seven women patients. It is evident that the administration of the drug to female patients was not done to cure erectile dysfunction. However, this drug was administered to seven female patients for a new indication as a possible drug for the treatment of Pulmonary Arterial Hypertension (PAH).

- 40.3 A question was asked regarding the same in the State Vidhan Sabha by MLA Paras Saklecha in Feb- April, 2011. In reply to this, Vidhan Sabha question numbered 6790 the Chief Minister of Madhya Pradesh Shri. Shiv Raj Chauhan stated:

"Tadalafil is being tested since 2005 for Pulmonary Hypertension. It was a pilot project and is a small case series and not a drug trial and that there was no need for obtaining permission from DCGI. It is only required to take approval of Institutional Ethics Committee".

It was further stated by the CM in the above mentioned reply, that no Clinical Liability Insurance was done in this case and no monetary grant was received for the testing. It was registered with the CTRI. The CM went on to say that:

"(d) on the website of Drug Controller General India, New Delhi, Tadalafil ' was approved as a new drug on 11-09-2003, for erectile dysfunction. On 14-11-2009 drug Tadalafil 20 mg was approved for Pulmonary Arterial Hypertension."

- 40.4 The drug was approved for treatment of PAH on 14-11-2009 for an additional indication but it was illegally tested on patients in MY Hospital since 2005 four years prior to its approval. Any administration of drug

- 40.5 Further, no liability insurance of any patient was done nor any statutory reports prescribed under the Rules of 1945 as amended was sent to DCGI, in violation of all the rules and procedures. There was no accountability in case of potential adverse effects. Since the entire trial was shrouded by the confidentiality clause, the reports regarding occurring of side effects could not be obtained.

- 40.6 When the trial of this drug began in Indore, simultaneous trials of this drug were conducted in the USA in Aug 2005. As this trial was not approved in India, no company could sponsor it. Therefore, MY Hospital became a sponsor. In the reply filed in response to RTI application it was stated that, the then Dean of the college was not aware that MY Hospital was projected as a sponsor of this drug trial.

- 40.7 The Implication of MY hospital being sponsor of trial are monetary as has been referred in the complaint of Dr Anand Rai and Veejay Chaudhary vide para 30 (V) of this petition. The rights to market the drug were given to CIPLA company which never was a sponsor of this drug trial. It caused a loss of Rs 500 crores to the sponsor i.e. MP Govt because MY hospital was the sponsor of this trial as per the CTRI registration.

Trials on Children Conducted in Chacha Nehru Bal Chikitsalaya

41. That clinical trials have been conducted on children in gross violation of consent procedure and without caring for their life and health. The details are as follows:

28.05.2011 to MLA of opposition, it was stated that from in the years 2006 to 2010, drug and vaccine trials on 1833 infants and children was carried out in Chacha Nehru Bal Chikitsalaya, Indore by Dr Hemant Jain. These trials raise a serious issue of "proxy" consent which violates the rights of the children and such consent is often taken by misrepresentation. As per the Economic Offences Wing report there were 18 serious adverse effects but information is not being disclosed by the Hospital. No investigation was carried out nor was any compensation given.

- 41.2 A complaint was filed Ajay Naik with the DCGI and Sanyogitaganj Police Station, Indore. In his complaint he has alleged that his 2 days old child, Yatharth Naik, was immunized with a trial vaccine. This was done in Chacha Nehru Bal Chikitsalaya, Indore without his knowledge by Dr Hemant Jain and Dr Ashish Dubey. In his affidavit, he has given the details of the trial conducted on his 2 days old child. His child was born on 08-03-2010 and on discharge was called back after 2 days. On 10-03-2010, he was told to sign some papers which were essential before giving the injection. At this stage he had no knowledge that a vaccine trial was being conducted on his child. The vaccine which was administered to his child could have had certain serious side effects high fever causing disability or death of which he was kept in the dark. Luckily, his child was saved from the serious adverse effects. On the 4th day child developed white spots all over the body for which the child was referred to skin specialist. Later when the issue was raised in the media, he came to know that vaccine trial was done on his 2 day old child.

- 41.3 It is pointed out that, most of trials on children are vaccine trials, meaning thereby, that they are conducted on healthy children who are disease free. The entire vaccine policy wherein the drug companies have been pushing their vaccines under the universal Immunisation Programmes for obtaining huge profits is a subject matter of investigation. The vaccine policy and the prospects of huge profits have stimulated a large number of vaccine trials even on new born and premature children, which is a very serious issue and needs to be checked/prohibited.

Trial of HPV vaccine on cervical cancer at Chacha Nehru Bal Chikitsalaya

42. Trial of Vaccine for HPV on Cervical Cancer was conducted in Indore inspite of the fact that similar vaccine trial which was conducted in Gujarat & Andhra Pradesh resulted in alleged deaths.
- 42.1 Trial of 'V-503 Multivalent vaccine' for Human Papilloma Virus (a causative agent of cervical cancer) was done in Indore and simultaneously in other cities. The trial was carried out by Dr Hemant Jain, who is professor of Paediatrics in Chacha Nehru Hospital, attached with MGM Medical College, Indore. He received a sum of Rs 4 lacs from a multinational drug company, Merck. The trial of multivalent V-503 was conducted on 39 girls, in the age group of 15 to 26. This trial was conducted despite the fact that a similar vaccine trial of Gardasil, was conducted in Andhra Pradesh and Gujarat, which had resulted in the deaths of 6 girls. The trial of Gardasil was stopped by the Government in all

42.2 However, the trial of the multivalent version of the same vaccine under name of V-503 commenced. It was stated that it was a phase IV trial and that vaccine was available in the market. This incident raises the following issues:

- a. How could a trial be conducted by Pediatrician on a subject related to gynecology?
- b. It was a phase III trial and not Phase IV trial as indicated by Dr Hemant Jain. There was no market approval. The vaccine available in market was V-501 and not V-503.
- c. This vaccine is not usable in Indian context. Cervical cancer is prevalent in women in late 40s and very rare in young women. The vaccine was tested on girls between the ages of 15-26 years.
- d. The vaccine when administered at the age of 10-15 yrs would not offer protection till beyond 40 years. The effect of vaccine does not last beyond 7 years and booster dose testing was not a part of trial.
- e. Further, HPV is not the only cause of cervical cancer, there are other causes like multiple sexual partners, use of oral contraceptives, poor hygiene, etc. Out of 15 strains identified for causing cervical cancer, vaccine offers protection only against 2 strains. The vaccine is only 70% effective in cases of HPV infection.
- f. According to WHO, the minimum threshold of antibodies for disease protection is not known. It is also not yet known "whether seropositivity (according to the thresholds

- g. The facility to detect cervical cancer (like Pap smear) is not available in Govt. Hospitals. The cost of 3 doses of vaccine is Rs 15000/- which is unaffordable for Indian patients. (*World Health Organization, 'Human Papilloma-virus and HPV vaccines: technical information for policy-makers and health professionals' WHO, 2007, pp 20*).
- h. The vaccine has reportedly caused 6 deaths in AP-Gujarat trials, one death in UK and serious adverse effects in 61 girls and 21 deaths in USA.
- i. Large commercial interests of Multinational US drug companies such as, Merck and GSK were involved in promoting the vaccine in universal immunization programme. This combined with the payment made to doctors, shows a serious violation of the conflict of interest clause in the ethical codes.

Trials on mentally ill patients:

43. That Indore also became the site for conducting clinical trials on psychiatric patients covering 15 protocols. The trials were conducted by 8 Government Psychiatrists who worked in Govt. MGM Medical College on 233 psychiatric patients in private clinics. Many of these clinics were not registered under the MP Clinic Registration Act. The trials included trial of a drug on premature ejaculation on 42 psychiatric patients, which is "unethical. The approval of Ethical Committees was obtained from unknown ethical committees. The ethical committees were not only of doubtful credentials but were located in far away smaller towns

Committees, Sidhant Ethical Committee, Ahmedabad, Manav Ethical Committee, Baroda, CHL ethical committee, Indore. The main issue raised in the psychiatric drug trials is that the subject in case of severe mental illness may not have the capacity to consent and "proxy" consents are taken. Another important issue is that even though the current law places a large responsibility on the Ethics Committees to oversee the safety of patients, such Ethics Committees cannot possibly play this role.

BHOPAL

44. That the other city in which legal clinical trials were conducted on the Bhopal Gas victims is the city of Bhopal. The following facts concerning Bhopal are relevant:
 - 44.1 Bhopal Memorial Hospital and Research Centre (BMHRC) was specifically built to help the victims of 1984 gas disaster by offering specialized treatment not available elsewhere. Under the pretext of helping them, the patients in this hospital were subjected to clinical trials. Between 2004 and 2008, over 160 patients of Bhopal Memorial Hospital were subjected to clinical trials on drugs including untested New Chemical Entities (NCEs) such as Prasugrel (approved: July 2009), Telavancin (approved: September 2009). Over 80% of the patients at BMH are Bhopal gas victims. Ethical guidelines prohibit clinical trials on subjects with "reduced autonomy." Bhopal gas victims have zero autonomy since they are totally dependent on treatment provided by the BMHRC. This raises a very important question: Can a gas-disaster victim refuse to take a drug prescribed by the doctor at the only

Ten patients died during these clinical trials. No compensation was paid to the families. This raises the question of why the DCGI and Ethics Committees approved such risky trials. Total amounts received from pharmaceutical companies in a four year period for conducting these trials came to Rs. 100,85,100.:

A few examples are

- AstraZeneca Ticagrelor trial Rs. 24,71,690
- Schering Momentasone trial Rs. 8,11,271
- GlaxoSmithKline Fondaparinux trial Rs. 5,74,809
- Wyeth Tigecycline trial Rs. 29,99,583
- Pfizer Ceftazidime trial Rs. 4,22,920
- Theravance Telavancin trial Rs. 8,86,000

- 44.2 Inspection of just three trials by Drugs Controller General, India (DCGI) has revealed that a great majority of those on whom new drugs were tested became seriously ill and were semi-literate patients. In the *Fondaparinux* trial, 42 out of 57 patients were gas-disaster victims. Six patients died during the trial. All deaths were dismissed as not "related to drug being tested" without any independent verification. Out of 57 patients, 49 could barely sign in Hindi.

- 44.3 In the Tigecycline trial, 32 patients out of 34 were gas disaster victims with three deaths during the trial. All deaths were categorized as "unrelated" to the use of investigational drug. Hence no compensation was paid. Out of 34 patients, 26 did not

- 44.4 In *Telavancin* trial, 5 out of 7 subjects enrolled died either during the trial or soon after. No one received any payment, either for participation in the trial or compensation for the death of a family member. The Hospital earned Rs. 6,23,820 because it spent only Rs. 2,62,180, out of Rs. 8,86,000 charged.
- Specifics of patient autonomy violations of the Bhopal Gas Victims can be found in a video report by Al Jazeera, Faultline: Outsourced Clinical Trials Overseas (This is also available on YouTube). The Petitioner is enclosing a CD (undated) of the Report by Al Jazeera as Annexure 19 (pages 934 to 935).

ANDHRA PRADESH

45. The following are the details of illegal HPV trials which were conducted in the state of Andhra Pradesh:
- 45.1 On 9 July 2009 and 13 August 2009, ICMR, PATH, AP Govt and Gujarat Govt. launched a project for vaccination of cervical cancer in adolescent girls. The vaccine used was Injection Gardasil of US firm Merck. In October 2009, a "Memorandum Highlighting Concerns Surrounding the Human Papilloma Virus (HPV) Vaccine" was submitted by 52 organisations and groups to the Union Minister for Health, Sh Gulam Nabi Azad, raising concerns against using the vaccine. There were reports of deaths of four girls following administration of vaccine in the Bhadrachalam division of AP in 2009 to Jan 2010. The very group which had raised the

30th March 2010. They took out a report titled, "Findings from visit to Bhadrachalam: HPV Vaccine Demonstration Project Site in Andhra Pradesh". Following the ethical concerns raised by various groups, the project was suspended by the MOHFW in April 2010. The Ministry appointed a Committee comprising of 6 members to enquire into the, "alleged irregularities in the conduct of studies using HPV vaccine by PATH in India" in April, 2010 vide notification no V.25011/160/2010-HR dated 15th April, 2010. The Committee submitted its final report on 15 February, 2011. A letter written by Rajya Sabha MP Brinda Karat raises serious issues concerning the trial and the Committee's report. True and correct copy of letter dated 09-05-2011 of Smt Brinda Karat, MP Rajya Sabha, addressed to the Union Health Minister are Annexures P 20. (935-943)

The Petitioner is also enclosing a true and correct copy of the memorandum of October, 2009 submitted by NGO groups and of "Findings from visit to Bhadrachalam: HPV Vaccine Demonstration Project Site in Andhra Pradesh" filed as Annexure P-21 (Colly) (pages 944 to 945).

- 45.2 The American charity PATH (Program for Appropriate Technology in Health) conducted Phase IV clinical trials of two foreign patented, and highly profitable HPV vaccines (Gardasil and Cervarix) on some 25,000 young girls belonging to the poor and illiterate families in Andhra Pradesh and Gujarat. The entire project was made to seem be of a philanthropic and educational nature to help India. PATH claimed that it was not a clinical trial

introduction of the HPV vaccine." It was not meant to assess efficacy or safety of the vaccines.

- 45.3 PATH obtained permission to conduct the study from Drugs Controller General, India (DCGI) by submitting protocol and other documents such as consent forms that are required for clinical trials, obtained approval from the Ethics Committees and actually vaccinated children. The protocol clearly listed the objectives: number, nature and percentage of vaccinated girls reporting serious and non-serious side effects.

- 45.4 PATH zeroed on four developing countries for the HPV trial: India, Peru, Uganda and Vietnam. During the trials in India, rules meant to safeguard the interests of participants were openly flouted. Some glaring examples of this are as follows:

- Trials were conducted on minors (10-14 year olds) without obtaining mandatory, informed consent from parents.
- Documentary evidence shows that in Andhra Pradesh, for example, in the case of 2,763 girls, consent documents were signed en bloc by teachers, hostel wardens, head masters etc.
- In another 1,948 cases, illiterate parents were asked to put thumb impressions on documents which they could not understand.
- In violation of Good Clinical Practice (GCP) and Indian

PATH, however, insured itself against such claims. As a result of this no compensation can be paid to the seven girls who died during the trials.

- In contravention of Indian regulations, there were no healthcare facilities (medical experts, hospitals, ICUs, drugs, equipment) available to deal with serious adverse effects and emergencies within reach of vaccination sites. Poor, vulnerable, helpless tribal girls in school hostels were predominantly used to collect data. Records show that in Andhra Pradesh, 26.47 per cent vaccinated girls were tribals while the state's tribal population is only 6.6 percent.
- Similarly in Gujarat, 26.56 vaccinated girls were tribals while the state's tribal population is 14.8 per cent. Manufacturers donated the vaccines worth Rs. 25 crores. The not so hidden agenda was to use the hype on prevention of cervical cancer generated by the project to get the vaccines included in the government funded Universal Immunisation Programme. With 1.25 crores girls becoming eligible for vaccination every year, the income of the manufacturers would swell by a whopping Rs. 11,250 crores every year (at Rs. 9,000 per girl).

PATH claims that it is funded by government and private sources. In its 2008 accounts, one of the sources of funding is stated to be "The Ministry of Health and Family Welfare, India." When asked, Health Minister Ghulam Nabi Azad told the Rajya Sabha (question

(already annexed as P-20) and Cervical cancer: trial & error' by CNN-IBN are annexed as Annexure P- 22 (pages 994 to 1000).

OTHER TRIALS

46. That the Petitioners are giving details of trials which were conducted in relation to certain specific drugs.

Letrozole Trial

- 46.1 Letrozole is an anti-cancer drug, which is contraindicated in young pre-menopausal women all over the world. (Ref: USFDA, MHRA, TGA-Australia), meaning thereby that the said drug should not be given. Studies in rats at doses equal to 0.003 mg/kg (about 1/100 the daily human dose on a mg/m2 basis) administered have shown letrozole is embryotoxic and fetotoxic. The Health Canada Warning states that:

'The drug has been linked to abortion, foetal or genetic defects and cancer when used to promote ovulation in women unable to conceive. Over 400 young women subjected to clinical trials to find out if this anti-cancer drug letrozole can help ovulation'.

The trials were conducted illegally without permission from the DCGI. These trials were conducted predominantly at private clinics which were not recognized as research centres. Results of these illegal trials were used extensively to promote the sale of letrozole; sale increased by 300% in just one year.

Erythromycin

- 46.2 That Erythromycin was tested in

approval and consent from participants. The findings of a clinical trial in West Bengal were published in "Contraception." The antibiotic erythromycin was reportedly inserted into the uteri of 790 rural women in two clinics in Calcutta and 24 South Parganas district without their informed consent. The aim of the study was to survey if erythromycin, which is commonly used for a variety of minor ailments, can be used as a form of contraception. Unfortunately, the failure rate was a high 28-35 per cent as claimed the study, jointly authored by Dr Biral Mullick and Dr Netal Bairagi. These trials were illegal and unethical, because the doctors neither applied for permission from the DCGI, nor did they have the informed consent of patients. No study of side effects was done, and the doctors illegally converted erythromycin, which is available in tablet form, into pellets in their own office. The erythromycin trials were allegedly carried out over a period of two years under the auspices of an NGO, the Calcutta-based Indian Rural Medical Association

Tide Trials

- 46.3 In 2007 global data showed that anti-diabetic agent *Rosiglitazone* had serious cardiac side effects compared to *Glipizide*. USFDA ordered GSK (the *Rosiglitazone* innovator) to conduct large scale trials on some 16,000 patients to confirm the findings. GSK faced problems in recruiting patients in the United States. In April 2010, more trial sites were added in developing countries such as India, Chile, Mexico, Colombia and Pakistan. The trial hardly had any

protests in India against this unethical trial, upon which they were suspended.

Safety concerns and other trials:

47. The petitioners are giving herein below a list of other trial which raised safety concern and ethical issues.

- Till 2005, trials of foreign drugs were permitted in India at one step below the Phase completed abroad. Yet DCGI approved Phase III trial of Pfizer's *Zoniporide*, even when Phase II trials had not been completed in USA. The carcinogenic and reproductive studies on animals mandated by Indian law had not been completed when approval was granted.
- *Ragaglitazar*: Human trials of Novo Nordisk's diabetes drug was suspended after a trial in mice revealed that the compound caused urinary bladder tumours.
- *Citalopram*: Dharmesh Vasava, 22, a healthy, paid "volunteer" from Bharuch in Gujarat died in a trial conducted by Sun Pharma. No compensation was given to him and his family.
- *Pneumococcal vaccine (Wveth)*: A baby with cardiac disorder was enrolled and died due to a trial being conducted on it. In this case study the Ethics Committee composition was unlawful.
- *Seroquel XR (AstraZeneca)*: This drug was tested at four centres in India. This was unethical since Quetiapine XR was tested against placebo while immediate release

approved by DCGI. Trial Results were accepted for approval of XR formulation.

- *Risperdal (Johnson & Johnson)*: Patients were deprived of current medication to determine the efficacy of trial drug. Their informed consent was not obtained.
- *Olympus endosuturing*: This device not only was tested on humans without animal testing. This was used on 13 patients in Delhi in a clinical trial. The hospital and investigator received US\$ 65,000 (Rs. 30 lacs) in this trial.
- Aside from this the drug *VEGF* was tested at the Metro Hospital, Noida, without regulatory approval *Betaxolol/TGFS (Alcon)* was also used without regulatory approval. *Pippalyadi Yoga* was tested at *AIIMS* without DCGI approval.

- III. That the Petitioners have not filed any other Writ Petition before this Court nor before any of the High Court claiming the reliefs as sought for in this Writ Petition.

- IV. The petitioner is filing the Writ Petition on the following, among other, grounds:

GROUND

- (a) Because clinical trials on human beings have, a direct impact on their health as well as their life. It is therefore, necessary that all precautions should be taken, through law and other regulations, to take care of the safety and transparency in clinical trials. These trials should not be conducted for such experimentations which

Declaration of Human Rights, 1948 and International Covenant on Civil and Political Rights, 1966 which emphasize on voluntary nature of treatment and informed consent, the 'Nuremberg Code' and the 'Helsinki Declaration', 1964 (as amended in 2008) lay down certain principles and guidelines for conducting clinical trials. In these guidelines, the interest of the patient and his well being as well as voluntary nature of informed consent have been given prime importance. These guidelines also lay down that due to economic reasons as well as medical vulnerability, a person should not be chosen for doing clinical trials. These trials ought to be based on fair and sound scientific principles. The petitioners submit the essential principles laid down in the international declarations/guidelines have been violated with impunity in our country.

- (b) Because the facts and evidence which have been gathered by the petitioners through the Report of EOW, Madhya Pradesh, Rajya Sabha Debates, Vidhan Sabha Debates, replies to RTI, Articles and other research materials etc point out that India is being used for conducting clinical trials by the multinational drug companies owing to the reason that the laws are not implemented strictly and that because of poverty and other economic reasons subjects for these trials are easily available. The Report of EOW clearly points out how independence of the ethical committees is compromised and the interests of patients are not safeguarded. Not only the most essential principle of informed consent is rampantly violated but the conflict of interest is clearly visible in

conduct of the clinical trials illegally and at the cost of health and lives of the people. They suffer from such weakness and loopholes that they are misused by the drug companies and doctors,

- (c) Because the Report by the Economic Offences Wing (EOW), Madhya Pradesh also points out that the for trials conducted on different patients the doctors earned huge money as well as availed foreign trips with their families. It is submitted that the clinical trials are meant for benefiting the public health and cannot be used as a business for making money by violating all legal and ethical concerns.
- (d) Because the facts / documents which have been put on record by the petitioners point out that neither Insurance cover was available to the trial subjects nor were they compensated for the adverse effects on individual's human health or death, as the case may be.
- (e) Because the facts / documents which have been put on record points out that the trials were conducted on the children as well as on the mentally ill patients in violation of the legal parameters as well as the guidelines Any in blatant violation of voluntary consent procedure.
- (f) Because the facts / documents mentioned in this petition also point out that the trials were conducted for certain drugs which were not required, particularly, on women and certain drugs were introduced which were harmful to their health.

submitted that the Ethics Committee has to be totally independent. Its members should not have any interest in the clinical trials which are conducted and that the sponsor of the trial should not provide any opinion in the matter related to the study. In practice, the Ethics Committee consists of the doctors of the same institution which are involved in conducting the clinical trial. Very often a doctor who is involved in the clinical trial also forms part of the Ethics Committee. In any case the decision is taken by the Doctors who are part of the same institutional set-up. Therefore, the Ethics Committee who take a decision with regard to conduct of clinical trials are not independent. A duration change is required in the constitution and functioning of Ethics Committee.

- (h) Because before granting approval for conducting clinical trial, Ethics Committee has to review the following documents (as per Appendix -VIII), but these documents are rarely available and/or reviewed by the Ethics Committee. The review of following documents is necessary before granting approval:
- (a) Trial Protocol (including protocol amendments), dated Version No.(s).....
- (b) Patients Information Sheet and informed Consent Form (including updates, if any) in English and / or vernacular language.
- (c) Investigator's Brochure, dated....., Version No.....
- (d) Proposed methods for patient accrual including advertisement(s) etc. proposed to be used for the purpose.

- (f) Insurance Policy/Compensation for participation and for serious adverse events occurring during the study participation.
- (g) Investigator's Agreement with the sponsor.
- (h) Investigator's Undertaking (Appendix VII)
- (i) Because the relevant provisions under the rules as amended up to date, are Section 21(b) which defines the term 'licensing authority' and Part XA which deals with "import or manufacture of new drug for clinical trial or marketing", consisting of Rule 122A, 122B, 122D, 122DA, 122 DAA, 122 DB, 122 DC, and 122E. These Rules have to be read with Schedule Y. The said Schedule refers to Appendix I to Appendix XI. Schedule Y mentions about application for permission, clinical trial, responsibilities of sponsors, responsibilities of investigators, informed consent, responsibilities of the ethics committee etc. Appendix I provide for the data which has to be submitted alongwith the application for conduct of clinical trials and Appendix II refers to the structure, contents and format for clinical study reports. After receiving this study report, the licensing authority grants permission. Rule 122 A & B authorizes the licensing authority to seek further information in case the data provided or generated is 'inadequate'. Therefore, the only power which has been given to the licensing authority is to look into the adequacy of the material. The licensing authority cannot refuse permission if it is not in public interest or the data has been generated or trial has been conducted in violation of Schedule Y and the Appendix. This is a very serious lacuna in the provisions and is resulting in grant of permission by the

'inadequate' used in Rule 122A is required to be read as including violation of legal provisions, guidelines, ethical norms etc.

- (j) Because the licensing authority ought to be a multimember body consisting of experts in medical science and other related fields who look into various medical and social aspects before granting permission to a new drug for marketing. The said Rule therefore, is not in consonance with right to health and life as provided under Article 21 of the Constitution. There should be known parameters on the basis of which the permission to a new drug can be granted or rejected. Either the licensing authority can be construed as multi member body or the said provision is to be held as not being in consonance with Article 21 of the Constitution.
- (k) Because the scrutiny of the application for conducting clinical trials and for granting approval to a new drug, ought to be done on the basis of known guidelines and scientific parameters. No such guidelines and scientific parameters exist. The mechanical application of mind would be clear from the fact that the Cilostazol trial for which application was made on 11th July 2002 was granted approval within 12 days i.e. on 26 July 2002. Similarly the clinical trial of Herceptin Vs. Arimidex for which application was made on 14.9.2002 and was granted clearance on 24.9.2002. This example has been mentioned in Annexure P-4. There are several instances in which clearances have been granted by licensing authority within a period of 7 to 15 days. It is incomprehensible that the data presented by the drug company

such a short period. It only shows that clearances are granted in a totally mechanical manner in the matter of such a serious nature.

- (l) Because there is no independent monitoring procedure. Whatever procedure which has prescribed under the Rules and Appendix is not only totally inadequate but is also not followed. It is necessary that there should be a transparent monitoring of the clinical trials and the entire data should be available in public domain.
- (m) Because in the present legal regime there is no provision of strict compliance of clinical trials and no penalty / punishment is provided for violating the Rules or Ethics /guidelines as provided in Annexure Y and related Appendix. This aspect would be clear from the fact that the doctors in Indore who violated the Rules were debarred from conducting clinical trials for six months. It is not known under which legal provision they were debarred. Further a fine of paltry sum of 5000/-, for conducting illegal clinical trial, imposed on 12 Doctors of Indore, is again very shocking. The fine has been imposed under the Madhya Pradesh Nursing Home and Clinical Establishment Act, (Registration and Licence) Act of 1973 (Amended in 2003) for not maintaining records of tests and treatment and not providing details to the CMO. These instances show that the doctors and other persons who are involved in conducting illegal clinical trial and playing with the lives of people go scot free because there is no provision to impose any penalty/punishment. This is the reason that multinational drug companies are finding India as a convenient place for conducting clinical trials.

Trials. The Pharmaceutical companies are under pressure to bring more new drugs into the market to be able to be profitable and cut on their drug development budget. Currently, about 50 % of clinical trials are outsourced to CROs. They being powerful stakeholders in the Clinical Trial business, it is a matter of concern that Indian Law does not even acknowledge their existence. There is no legal framework for registration or monitoring of the CROs.

- (n) That the Petitioners crave leave to add such other further grounds as may be required.

PRAYER:

The petitioners pray that in the facts and circumstances of the present case, this Hon'ble court may be pleased to issue a writ of Mandamus/Certiorari or a Writ or Direction of like nature directing/ granting the following prayers:

- (i) Direct the respondents to inquire/ Investigate Into all the cases of adverse effects of clinical trials on the people resulting in disability and/or death throughout the country, by including such experts for such inquiry/ investigation as this Hon'ble Court deems it fit and proper and submit its report to this Hon'ble Court for appropriate directions and register criminal cases against the offenders

- (ii) Direct that a complete status of clinical trial implementation in the country be provided by the Respondents.
- (iii) Declare that Rule 122A(2) and 122B(2A) which provide that Licensing Authority shall examine only 'inadequacy' of the data furnished for grant of approval to a new drug as well as examination of this data by Licensing Authority mentioned under Rule 21(b) which consists of a single member and not a multi-member expert committee, are unconstitutional, not being in consonance with Article 21 of the Constitution.
- (iv) Direct the respondents to constitute of an expert committee to examine the present legal set-up and guidelines concerning the clinical trials including all short-comings, lacuna, violations etc and submit recommendations to enable this Hon'ble Court to frame guidelines for protection of right to life and health, under Article 21 of the Constitution.
- (v) Direct that the Govt. of Madhya Pradesh should act on the Report dated 24.6.2011. of the Economic Offences Wing [EOW] of the Madhya Pradesh Government by taking appropriate action against the Government Departments/ Officials/ Doctors and others who are involved in the illegal trials;
- (vi) Direct the respondents to grant of such compensation and other reliefs, including medical treatment, to the persons adversely affected

(vii) Pass such other order and or direction as this Hon'ble Court deem fit and proper in the facts and circumstances of the present case.

FILED BY:

Settled by: Sanjay Parikh, Advocate

[PUKHRAMBAM RAMESH KUMAR]
ADVOCATE FOR THE PETITIONER

Drawn on: 5.1.2012
Filed on: 7.1.2012
New Delhi

Appendix II.

Variables considered in the 2010 study conducted by Shah and colleagues

The favourable factors included the following variables in the participant responses:

Note: these have been grouped as such by the authors of the study (Shah et al., 2010)

Personal Health Benefits: Less chance of getting infected with HIV; Protection from HIV; HIV vaccine is very important for self; HIV vaccine is somewhat important for self; If they had a terminal illness; If they thought the drug would cure them; If an active drug is received instead of placebo; If the drug/treatment would help me; If there were no other medical options available to me; May help themselves with the condition; Relief from pain; Level of protection from dose.

Altruism: Somewhat likely belief in the success of AIDS vaccine; Vaccine for control of AIDS epidemic in India; If the drug/treatment would help someone else in the future; Help advance science and find a cure for diseases/conditions; May help save lives; Allows helping others with the condition; Allow medical team to find an effective treatment; Help medical community. Participation is important for the common good of India; Help researchers prevent HIV/AIDS; There will be an effective HIV vaccine in a few years; HIV will become preventable like polio; Even if the vaccine does not work, help researchers find an effective vaccine; Help researchers prevent HIV/AIDS.

Methods for motivating participation: Where was the information about trial given? Whether information was provided through government owned television channels; whether information given during healthcare camps, whether personal physician gave the information about the trial; information received through family, friends, relatives, or awareness programs such as AIDS leaflets. Whether the trial participant relied on research institutes for providing information regarding safety; Email notifications; Internet; Harris interactive; Awareness of the HIV Vaccine Trials Preparations in India; Awareness of Vaccination Priorities.

Source of Extra Income/Benefits: Insurance; If money is received for participation; Free medication is provided.

Detailed knowledge about trials: Included complete and detailed information about risks, knowledge of vaccines, technical terminologies explained and knowledge of HIV vaccinations (for HIV related trials).

Trust in Physicians: Preferred to rely on specific health care providers (family doctors, counsellors) for providing information regarding safety; Belief that doctors only do good.

Appendix II.

Variables considered in the 2010 study conducted by Shah and colleagues

<p>The factors acting as barriers included the following variables in the participant responses:</p> <p>Note: these have been grouped as such by the authors of the study (Shah et al., 2010)</p>
<p>Mistrust in trial organisations: Worry about mode of treatment i.e. whether given vaccine or placebo; Do not want to take drugs without treating doctor's permission; Are like guinea pigs; Are taking a gamble with their health.</p>
<p>Concerns about efficacy and safety of trials: Side effects of vaccine/not sure of safety; Long-term effect of vaccine; Concern about safety procedure; Unknown efficacy of vaccine; Concern about effects of a HIV vaccine on participant's lives; Possible unknown long-term side effects of vaccine; Possible side effects; Health risks; Unproven therapy.</p>
<p>Dependency Issues: Difficult to decide in anticipation; Lack of privacy at home; Lack of supportive network/family commitments; Peer family pressure; Social support; Not able to make independent decision.</p>
<p>Loss of confidentiality/ Privacy Concerns: Effect on insurance, marriage or getting a job; Privacy concerns.</p>
<p>Trial Burden: Time constraint; Effect on travel; Did not want to take new drugs; Unnecessary tablets; Wanted to go home.</p>
<p>Psychological Reasons: Fear of injection; Afraid of tests; Fear of stigma, General disinterest in volunteering.</p>
<p>Language: Do not understand the language.</p>

Informed Consent Form (Hindi)

रैनबैक्सी लेबोरेट्रीज़ लिमिटेड

पृष्ठ 1/7

सूचित सहमति पत्र - A

क्लीनिकल फार्माकालोजी यूनिट, रैनबैक्सी लैब्स लिमिटेड में स्वस्थ व्यस्क मानव स्वयंसेवकों में करे जाने वाले जैव उपलब्धी/जैव उपलब्धी की समानता के एक अध्ययन के बारे में सामान्य जानकारी

प्रिय स्वयंसेवक,

यह दस्तावेज जैव उपलब्धी/जैव उपलब्धी की समानता के एक अध्ययन में भाग लेने के लिये ज़रूरी जानकारी/सूचना आपको प्रदान करने के लिये तैयार किया गया है। कृपया इस जानकारी/सूचना को ध्यान से पढ़ें और इस अध्ययन में भाग लेने का निर्णय लेने से पहले यदि आपका कोई भी प्रश्न हो तो तो उसका स्पष्टीकरण करा लें।

- यह एक रिसर्च/अनुसन्धान करने वाला अध्ययन है। आपको इस रिसर्च अध्ययन में भाग लेने के लिए पूछा जा रहा है।
- इस अध्ययन में भाग लेने के लिए सहमत होने से पहले आप इस जानकारी/सूचना को ध्यान से पढ़ें तथा समझ लें। यह करने के लिये आप अपना पूरा समय लें।
- यदि आप इस दस्तावेज का कोई हिस्सा समझने में असक्षम हैं, तो अपने सभी प्रश्नों का स्पष्टीकरण/उत्तर प्राप्त करने के लिये आप पूरी तरह से स्वतन्त्र महसूस करें। इस दस्तावेज के बारे में आपको मौखिक जानकारी भी प्रदान करी जाएगी। यह मौखिक जानकारी आपको उस भाषा में दी जायेगी, जिसे आप समझते हैं।
- कृपया सूचित सहमति पत्र (A तथा B) पर हस्ताक्षर करें और इसे हमारे रिकार्ड के लिए जमा करें। आपके संदर्भ और यादगार के लिए आपको इसकी एक कॉपी प्रदान करी जायेगी।
- इस अध्ययन में भाग लेने के दौरान आप एक निष्पक्ष व्यक्ति की भांति होंगे तथा रैनबैक्सी लेबोरेट्रीज़ लिमिटेड के एजेंट/प्रतिनिधि, भागीदार/साझेदार अथवा कर्मचारी नहीं होंगे।

स्वयंसेवक के हस्ताक्षर _____

अध्ययन का उद्देश्य

दवा का सेवन करने के बाद शरीर (उदाहरण के लिये रक्त, मूत्र) में उपलब्ध होने वाली दवा की मात्रा को जैव उपलब्धी कहते हैं। दो दवाईयों की जैव उपलब्धी को समान कहा जाता है यदि इन दवाईयों का सेवन करने के बाद शरीर (उदाहरण के लिये रक्त, मूत्र) में उपलब्ध होने वाली दवा की मात्रा एक समान है।

बाजार में बिक रही दवा (जिसे रैफरैन्स कहते हैं) तथा भविष्य में बेची जाने वाली जैनेरिक दवा (जिसे टैस्ट कहते हैं) के बीच जैव उपलब्धी की समानता को सिद्ध करना पड़ता है। सरकार की एजैन्सियों जैव उपलब्धी की समानता के लिये हुए अध्ययनों के परिणामों को विस्तार और ध्यानपूर्वक जाँचती हैं। जब वे सन्तुष्ट हो जाती हैं कि दोनों फार्मुलेशनों एक समान (जैव उपलब्धी में एक समान) हैं तो टैस्ट दवा को बिक्री के लिए स्वीकृति दी जा सकती है।

जैव उपलब्धी/जैव उपलब्धी की समानता के अध्ययन की सामान्य प्रक्रिया

जैव उपलब्धी/जैव उपलब्धी की समानता का अध्ययन कैसे आयोजित किया जाता है, इसका एक सामान्य स्पष्टीकरण/विवरण नीचे दिया है।

यदि आप चुनाव की जाँचों में ठीक पाये जाते हैं तथा अध्ययन में भाग लेने के लिये लिखित सूचित सहमति देते हैं, तो आपको अध्ययन में दाखिल किया जायेगा। अध्ययन की प्रत्येक अवधि में दाखिले के दिन शराब अथवा अल्कोहल के लिये सॉस की जाँच, नशे की दवाईयों की मूत्र जाँच तथा अध्ययन आदिलेख (प्रोटोकाल) में बतायी अन्य जाँचें करी जायेंगी। दाखिले से पहले आपके सामान और आपकी जेबों की जाँच करी जायेगी तथा आपको शराब/अल्कोहल, जैन्थीन (xanthine), तम्बाकू, सिगरेट, गैरकानूनी दवाईयों, किसी भी प्रकार की कोई दवा, कोई भी खाद्य पदार्थ (ठोस और तरल) तथा विद्युत/बिजली अथवा बैटरी से चलने वाला कोई भी यन्त्र/उपकरण (कलाई पर पहनने वाली घड़ी और बिना कैमरे वाले मोबाइल फोन को छोड़ कर) लाने की आज्ञा नहीं होगी। यूनिट में आपके ठहरने की अवधि के दौरान आपको रैनबैक्सी द्वारा स्वयंसेवकों के कपड़े/वरदी प्रदान करे जायेंगे। इस अध्ययन में आपके भाग लेने की अवधि के दौरान अपना सामान रखने के लिये आपको लौकर प्रदान किया जायेगा तथा आपको एक पहचान पत्र दिया जायेगा जिसे यूनिट में ठहरने के दौरान आपको प्रदर्शित करके रखना होगा। सी0 पी0 यू0 में आपके ठहरने की अवधि के दौरान आप पर समीप परिधि वाले टी0 वी0 कैमरे के माध्यम से नज़र रखी जा सकती है।

स्वयंसेवक के हस्ताक्षर _____

यूनिट में ठहरने के दौरान आपको मानक भोजन प्रदान किया जायेगा (भोजन के विस्तृत विवरण के लिये सूचित सहमति पत्र - B में दिये अध्ययन सारांश को देखें)।

अध्ययन की प्रत्येक अवधि में आपको अध्ययन दवाईयों (टैस्ट अथवा रैफरैन्स) में से एक दवा का सेवन करना होगा।

अध्ययन आदिलेख (प्रोटोकाल) के अनुसार रक्त के नमूने पहले से निर्धारित समय के अन्तरालों पर वैक्यूटेनरों/ट्यूबों में लिये जाएंगे। रक्त संग्रह एक डिस्पोजेबल सुई और नली द्वारा किया जाएगा जो एक नाड़ी (नस) में प्रविष्ट की जाएगी और उसी स्थान पर लगी रहेगी। सुई का छेद बन्द न हो जाए इसके लिए हैपारीन (जो एक साधारण शरीर घटक है) का बहुत पतला घोल दिया जाएगा। नमूना लेने से पहले आधा मिलीलीटर हैपारीनयुक्त रक्त अलग फेंक दिया जाएगा। इसके अलावा सीधे विसंक्रमित सुई और सिरीज से भी एक के बाद एक रक्त के नमूने लिए जा सकते हैं। आगे के विश्लेषण के लिये एकत्र करे गए नमूनों को उचित स्थान पर प्रोसेस और स्टोर/संग्रहित किया जायेगा (नमूने एकत्र करने के समय बिन्दुओं के विवरण के लिये सूचित सहमति पत्र - B देखें)।

अध्ययन की आवश्यकताओं के अनुसार अन्य जैविक नमूने (उदाहरण के लिये मूत्र, मल, बलगम के नमूने) पूर्व निर्धारित समय के अन्तरालों पर लिये जा सकते हैं।

अध्ययन के दौरान किए गए रक्त संग्रहों से कभी-कभी हाथ में दर्द, सूजन तथा/अथवा सुन्नता के लक्षण आ सकते हैं। इससे कभी कभी सिर चकराने अथवा मूर्च्छा आने जैसी प्रतिक्रियाएं उत्पन्न हो सकती हैं। ये प्रतिक्रियाएं आमतौर पर कम समय के लिए और प्रतिवर्ति/वापस ठीक हो जाने वाली होती हैं।

यूनिट में ठहरने की अवधि के पूरा होने के बाद आपकी यूनिट से छुट्टी करी जायेगी तथा आपको एक विशिष्ट दिन एक विशिष्ट समय पर यूनिट में वापस आने की हिदायत दी जायेगी, अध्ययन की अगली अवधियों के लिये अथवा यूनिट में आकर नमूने देने के लिये अथवा अध्ययन के समाप्त होने पर सुरक्षा नमूना देने के लिये, वाइटल्स नपवाने के लिए तथा दुष्प्रभाव नोट करवाने के लिए (यदि जरूरत होगी तो)।

अध्ययन की अगली अवधियों में समान प्रक्रियाओं का पालन किया जायेगा, सूचित सहमति लेने की प्रक्रिया को छोड़ कर।

पालन करने वाले प्रतिबन्ध

यदि आप इस अध्ययन में स्वयंसेवक के रूप में भाग लेते हैं तो आपको कुछ प्रतिबन्धों का पालन करना होगा:

यूनिट में आपके ठहरने की अवधि के दौरान आपको चाय, कॉफी, चाकलेट तथा कोला का सेवन करने की आज्ञा नहीं होगी। अध्ययन शुरू होने के 48 घण्टे पहले से लेकर अध्ययन के दौरान फार्माकोकाइनेटिक (pharmacokinetic यानी रक्त में ओषधि की मात्रा से सम्बन्धित) जाँच के लिये अन्तिम नमूना एकत्र करने की अवधि तक आप किसी भी प्रकार की शराब अथवा शराब या अल्कोहल युक्त पदार्थ (पेय पदार्थ, मैरीनैड, दवा, इत्यादि), ग्रेपफ्रूट (grapefruit; एक प्रकार की छोटी नारंगी) का रस तथा/अथवा ग्रेपफ्रूट संपूरक (grapefruit supplement) का सेवन नहीं करेंगे। अध्ययन से 30 दिन पहले की अवधि के दौरान तथा अध्ययन की अवधि के दौरान यह ज़रूरी है कि आप किसी भी दवा (जिसमें ओ0 टी0 सी0 दवाईयों शामिल हैं) का सेवन नहीं करेंगे। दवा का सेवन करने से पहले तथा दवा का सेवन करने के बाद आपको पीने का पानी लेने से सम्बन्धित प्रतिबन्धों का पालन करना होगा। अध्ययन दवा की खुराक लेने के बाद आपको मुद्रा सम्बन्धी प्रतिबन्ध का पालन भी करना होगा (पीने का पानी लेने तथा मुद्रा सम्बन्धी प्रतिबन्धों के विशिष्ट विवरण के लिये कृपया सूचित सहमति पत्र B देखें)।

लाभ

आपको अध्ययन दवा (दवाओं) के उपचार की बिल्कुल भी आवश्यकता नहीं है इसलिए पीड़ित व्यक्तियों की सेवाहित किए जाने वाले कार्य से मिलने वाले मानसिक संतोष तथा मुफ्त स्वास्थ्य जाँच के अलावा आपको इस अध्ययन से कोई और चिकित्सा लाभ नहीं होगा।

नई जानकारी

कोई भी नई तथा महत्वपूर्ण जानकारी जिसका ज्ञान अध्ययन के दौरान होता है तथा जो आपके द्वारा अध्ययन जारी रखने की सहमति पर प्रभाव डाल सकती है, से आपको जल्दी से जल्दी अवगत कराया जाएगा।

वैकल्पिक उपचार

क्योंकि यह अध्ययन अनुसंधान के लिए किया जा रहा है, इसलिए दूसरा उपलब्ध रास्ता यही होगा कि आप इस अध्ययन में भाग न लें।

इन्श्योरेंस (insurance) यानी बीमा नीति

बजाज एलीएन्ज़ (Bajaj Allianz) की बीमा (insurance; इन्श्योरेंस) नीति संख्या OG-10-1113-3306-00000004 के अन्तर्गत आपका बीमा कराया गया है तथा अध्ययन से सम्बन्धित चोट लगने की स्थिति में आपको क्षतिपूर्ति प्रदान करी जायेगी।

अनुशासन

आपसे यह उम्मीद की जाती है कि आप सी० पी० यू० में ठहरने के दौरान सी० पी० यू० के कुछ नियमों का पालन करेंगे तथा सी० पी० यू० में अनुशासन बनाये रखेंगे। अगर आप सी० पी० यू० में उचित व्यवहार नहीं करते हैं तो आपको बिना कोई भुगतान किये आपको इस अध्ययन से निकाला जा सकता है तथा/अथवा आपको आगे के अध्ययनों में हिस्सा लेने से रोका जा सकता है।

अध्ययन पूरा न कर पाने की स्थिति में वित्तीय क्षतिपूर्ति निर्धारण

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|---|---|
| 1. अध्ययन दवा दिये जाने से पहले आपकी सेहत को ध्यान में रखते हुए जॉचकर्ता द्वारा अध्ययन से हटाये जाने पर | यथानुपात आधार पर |
| 2. अध्ययन दवा दिये जाने के बाद आपकी सेहत को ध्यान में रखते हुए जॉचकर्ता द्वारा अध्ययन से हटाये जाने पर | पूरा भुगतान, अध्ययन समाप्त होने/अनुकरण पूरा होने पर |
| 3. अध्ययन दवा दिये जाने के बाद आपकी अपनी मर्जी के अनुसार अध्ययन छोड़ने पर | यथानुपात आधार पर |
| 4. जॉचकर्ता की आज्ञा से किसी उचित कारणवश अध्ययन छोड़ने पर | यथानुपात आधार पर |
| 5. अध्ययन आवश्यकताओं पर पूरा न उतर पाने की स्थिति में जॉचकर्ता द्वारा अध्ययन से हटाए जाने की स्थिति में | यथानुपात आधार पर |

स्वयंसेवक के हस्ताक्षर _____

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| 6. आपके द्वारा जानबूझ कर अपनी किसी बीमारी जो कि इस अध्ययन से संबंध रखती हो के बारे में जानकारी छुपाने की स्थिति में जॉचकर्ता द्वारा अध्ययन से हटाए जाने पर | कोई भुगतान नहीं |
| 7. अनुकरण के निर्धारित समय पर अनुकरण के लिये यूनिट में न आने पर (जहाँ लागू हो) | अनुकरण के लिये निर्धारित रकम का आधा |

गोपनीयता

जहाँ तक कानून अनुमति दे इस अध्ययन में आपके भाग लिए जाने के रिकार्ड गुप्त रखे जाएंगे। परन्तु गुप्त कागजात जो आपकी पहचान आपके नाम द्वारा करते हैं अध्ययन अधिकारी को, जॉच के समय कौरपोरेट गुणवत्ता जॉचकर्ता को तथा इन्सटीट्यूशनल रिव्यू बोर्ड (आई0 आर0 बी0) को और अन्य नियंत्रण संस्थाओं को जरूरत पड़ने पर उपलब्ध होंगे। अगर यह जानकारी किसी भी प्रकार से प्रकाशित होती है तो उसमें आपका नाम नहीं होगा। जब तक अध्ययन सम्बन्धी ऑकड़ों/दस्तावेजों को जमा करने के लिये नहीं भेजा जाता है, जॉचकर्ता का प्रतिनिधि अथवा जॉचकर्ता द्वारा नियुक्त व्यक्ति इस अध्ययन के ऑकड़ों का रक्षक होगा।

चोट/अस्वस्थता के लिए उपचार

किसी भी अध्ययन सम्बन्धी दुष्प्रभाव की स्थिति में चिकित्सा सम्बन्धी सहायता क्लीनिकल फार्माकालोजी यूनिट में उपलब्ध करवाई जाएगी और दुष्प्रभावों के उपचार के लिए अस्पताल ले जाए जाने की जरूरत पड़ने पर आपको पास ही के अस्पताल में ले जाया जाएगा और इसका सारा खर्चा रैनबैक्सी लेबोरेट्रीज़ लिमिटेड उठाएगी।

भाग लेने का स्वैच्छिक स्वरूप

आप इस अध्ययन में अपनी इच्छा से भाग लेने के लिए या भाग लेने से इन्कार करने के लिए पूरी तरह से आजाद हैं। आप इस अध्ययन में भाग लेने के लिये सहमत होते हैं अथवा इससे इन्कार करते हैं, इससे आप पर कोई जुर्माना नहीं होगा और न ही आगे होने वाले अध्ययनों में आपके भाग लेने पर कोई प्रभाव नहीं पड़ेगा। आप किसी भी समय इस अनुसंधान में भाग लेने से हट सकते हैं। यह आपकी अपनी पसन्द है तथा आपके सभी अधिकारों का सम्मान किया जायेगा।

स्वयंसेवक के हस्ताक्षर _____

नोट: निम्न अवस्थाओं के ज्ञात होने पर जाँचकर्ता आपको इस अध्ययन में भाग लेने से रोक सकते हैं: अध्ययन में भाग लेना आपके स्वास्थ्य के लिये हानिकारक प्रतीत होता है, आप अध्ययन आवश्यकताओं को पूरा नहीं कर पाते हैं, आपने अपने चिकित्सा इतिहास संबंधी जानकारी छुपाई है, अथवा अध्ययन को रद्द कर दिया जाता है।

किसी भी आपातकालीन स्थिति में आप अध्ययन कर्मचारियों को भी आपातकालीन घन्टी बजा कर बुला सकते हैं। यह आपातकालीन घन्टी वॉर्ड और शौचालय कक्ष/क्षेत्र में लगी हुई है।

सम्पर्क सम्बंधी जानकारी

इस अध्ययन के बारे में और अधिक जानकारी आप इस अध्ययन से पहले, इसके दौरान या बाद में कभी भी प्राप्त कर सकते हैं। अध्ययन के दौरान आपकी सेहत से सम्बन्धित किसी भी आपातकालीन स्थिति में या अध्ययन से होने वाली असुविधा या चोट सम्बन्धी प्रश्नों के उत्तर जानने के लिए कृपया जाँचकर्ता से इस पते पर सम्पर्क करें: रैनबैक्सी क्लीनिकल फार्माकालोजी यूनिट, माजीदिया अस्पताल, दूसरी मंजिल, हमदर्द नगर, नई दिल्ली - 110062, टेलीफोन : 2995-6721

अनुसंधान में भाग लेने वाले स्वयंसेवक के रूप में अपने अधिकारों के बारे में अगर आपका कोई प्रश्न है तो जानकारी लेने के लिए आप डा० फरहान जालीस एहमद, संयोजक/सदस्य सचिव, जामिया हमदर्द इंस्टीच्युशनल रीवीयु बोर्ड (टेलीफोन नम्बर 9810720387) से सम्पर्क कर सकते हैं।

नोट: अध्ययन के दौरान किसी भी समय आप अपने निजी/ पारिवारिक डाक्टर की सलाह भी ले सकते हैं।

सूचित सहमति पत्र – B (अध्ययन की जानकारी)

स्वस्थ व्यस्क मानव पुरुष स्वयंसेवकों में खाना खाने के बाद की अवस्था में रैनबैक्सी लेबोरेट्रीज़ लिमिटेड की दो बैचिस (batches; वर्गों) की ओलोपैटाडीन हाइड्रोक्लोराइड 10 मि० ग्रा० दीर्घ निस्तार होने वाली गोली (olopatadine hydrochloride 10 mg extended release tablet) की मुख द्वारा दी गई एक खुराक के साथ एलीलौक 5 मि० ग्रा० गोलियों (ALLELOCK® 5 mg tablets) की मुख द्वारा दी गई दो खुराकों पर तुलनात्मक जैव उपलब्धी का अध्ययन।

विवरण : 01
तारीख : 16 जुलाई 2010।
सुपरसीड्स : लागू नहीं।

यह दस्तावेज जैव उपलब्धी के इस अध्ययन के बारे में जानकारी/सूचना प्रदान करता है। इस अध्ययन में भाग लेने का निर्णय लेने से पहले कृपया आप इस जानकारी/सूचना को पढ़ें और अपने सभी सन्देहों का स्पष्टीकरण लें। अगर आप इस अध्ययन में भाग लेने के लिये सहमत होते हैं, तो दस्तावेज पर हस्ताक्षर करें तथा हमारे रिकार्ड के लिए जमा करा दें।

यह अध्ययन प्रत्येक अवधि में ओलोपैटाडीन हाइड्रोक्लोराइड 10 मि० ग्रा० (olopatadine hydrochloride 10 mg) युक्त दीर्घ निस्तार होने वाली गोली (extended release tablet) की फार्मुलेशन की एक खुराक को अथवा एलीलौक 5 मि० ग्रा० गोलियों (ALLELOCK® 5 mg tablets) की दो खुराकों (प्रत्येक खुराक में ओलोपैटाडीन हाइड्रोक्लोराइड 5 मि० ग्रा० है, जिन्हें 12 घंटे के अन्तराल पर दिया जायेगा; कुल खुराक 10 मि० ग्रा०) को देने के बाद रक्त में दवा की मात्रा जांचने के लिए किया जाने वाला अनुसंधान है।

ओलोपैटाडीन (olopatadine) एक सलेक्टिव हिस्टामीन एच-1 रिसैप्टर एन्टागोनिस्ट दवा (selective histamine H1-receptor antagonist) है, जिसमें मानव पौलीमोर्फोन्युक्लीयर ल्युकोसाइट कणों (polymorphonuclear leukocytes) तथा ईओसिनोफिल कणों (eosinophils) से ल्युकोट्राइन (leukotriene) और थ्रोम्बोक्सेन (thromboxane) जैसे सूजन उत्पन्न करने वाले लिपिड मध्यस्थों (inflammatory lipid mediators) के निस्तार पर निरोधात्मक प्रभाव डालने की क्षमता होती है। इस दवा को निम्न

स्वयंसेवक के हस्ताक्षर _____

अवस्थाओं के इलाज के लिये इस्तेमाल किया जाता है: एलर्जिक राइनायटिस (allergic rhinitis; एलर्जी के कारण होने वाली नाक की सूजन/नाक बहना), अर्टिकेरीया (urticaria; त्वचा पर चकत्ते निकलना), त्वचा रोगों [जैसे छजन (eczema)/त्वचा की सूजन, खुजली वाले दाने, खुजली, त्वचा का सोरीएसिस (psoriasis; एक प्रकार का चर्मरोग), वल्गैरिस (vulgaris; त्वचा की सूजन वाला एक रोग), मल्टीफॉर्म एग्जुडेटिव ईरीथिमा (multiform exudative erythema)] के कारण होने वाली खुजली।

तीन अवधियों वाले इस अध्ययन में रैनबैक्सी लेबोरेट्रीज लिमिटेड, भारत की दो बैचिस (batches; वर्गों) की ओलोपैटाडीन हाइड्रोक्लोराइड 10 मि0 ग्रा0 दीर्घ निस्तार होने वाली गोलियों (olopatadine hydrochloride 10 mg extended release tablets) की मुख द्वारा दी गई एक खुराक की तुलना क्योवा हक्को कोगियो कम्पनी लिमिटेड, जापान (Kyowa Hakko Kogyo Co. Ltd., Japan) के रैफरैन्स प्रोडक्ट, एलीलोक 5 मि0 ग्रा0 गोलियों (ALLELOCK® 5 mg tablets) की दो खुराकों (प्रत्येक खुराक में ओलोपैटाडीन हाइड्रोक्लोराइड 5 मि0 ग्रा0 है, जिन्हें 12 घंटे के अन्तराल पर दिया जायेगा; कुल खुराक 10 मि0 ग्रा0) के साथ 15 स्वस्थ व्यस्क मानव पुरुष स्वयंसेवकों में खाना खाने के बाद की अवस्था में करी जायेगी।

दुष्प्रभाव

आम तौर पर बताये गए दुष्प्रभाव जिगर की कार्य क्षमता से सम्बन्धी रोग हैं, जिनमें निम्न शामिल हैं: एस0 जी0 ओ0 टी0 (SGOT), एस0 जी0 पी0 टी0 (SGPT), गामा जी0 जी0 टी0 (γ-GGT), एल0 डी0 एच0 (LDH) तथा ए0 एल0 पी0 (ALP), इत्यादि के स्तर में बढ़त होना, पीलिया (jaundice; जौन्डिस) होना तथा निन्द्रालुता। क्लीनिकल अध्ययनों के दौरान बताये जाने वाले अन्य दुष्प्रभाव, जिनके घटन की आवृत्ति < 5% तथा ≥ 0.1% थी, इस प्रकार हैं:

- दाने निकलना, जिसमें ईरीथिमा (erythema; त्वचा की लालिमा) शामिल है, सूजन आना (मुँह, हाथ पैरों, इत्यादि पर)।
- अस्वस्थता होना, चक्कर आना, सिर में दर्द होना, सिर में मन्द दर्द होना, प्यास लगना।
- पेट में परेशानी होना, पेट में दर्द होना, दस्त लगना, जी मिचलाना।
- रक्त के श्वेत कणों की गणना में अत्याधिक बढ़त होना, रक्त के श्वेत कणों की गणना में अत्याधिक कमी होना, रक्त के ईओसिनोफिल कणों (eosinophils) की गणना में अत्याधिक बढ़त होना, रक्त के लिम्फोसाइट कणों (Lymphocytes) की गणना में अत्याधिक कमी होना,

नोट: आप इस अध्ययन में भाग ले सकते अगर आपके हीमोग्लोबिन का स्तर 13.0 ग्राम/प्रति डी0 एल0 (13.0 g/dl) के बराबर अथवा उससे अधिक है।

आप इस अध्ययन में भाग नहीं ले सकते हैं अगर आपको:

- आपको ओलोपैटाडीन (olopatadine) अथवा किसी भी अन्य सम्बन्धित दवाई से हायपरसैन्सिटिविटी (hypersensitivity) अथवा एलर्जी होने का इतिहास है।
- आपको लम्बे समय से सिर में दर्द होने का इतिहास है।
- इस अध्ययन से एक सप्ताह पहले की अवधि में आपको पेट में परेशानी होने, दस्त लगने तथा/अथवा जी मिचलान का इतिहास है।
- आपको जिगर की कार्य क्षमता से सम्बन्धी रोग होने तथा/अथवा पीलिया (jaundice; जौन्डिस) होने का इतिहास है।
- आपको किसी भी निन्द्रा सम्बन्धी रोग होने का इतिहास है।
- आपको दवा के कारण त्वचा पर खुजली होने तथा/अथवा दाने निकलने का इतिहास है।

नोट:

- अगर आप बीमार महसूस करें अथवा व्याकुलता/बैचैनी का अनुभव करें तो कृपया ड्यूटी पर मौजूद चिकित्सक/नर्स/अधिकारी को तत्काल सूचित करें।

सावधान:

अध्ययन की अवधि के दौरान आप किसी मशीन पर काम न करें अथवा कोई वाहन न चलायें।

वित्तीय क्षतिपूर्ति

इस अध्ययन में अध्ययन को पूरा करने वाले प्रत्येक स्वयंसेवक को 7,250/- रुपये (सात हजार दो सौ पचास रुपये मात्र) क्षतिपूर्ति के रूप में दिए जाएंगे। इसमें से 500/- रुपये (पाँच सौ रुपये) की रकम आपको अध्ययन के समाप्त होने पर होने वाली सुरक्षा जाँचों के सन्तोषजनक रूप से पूरा होने के बाद दी जायेगी। यह क्षतिपूर्ति आपको अध्ययन के दौरान होने वाली असुविधा तथा पीड़ा के बदले दी जाएगी।

अगर दाखिले के समय आप अपने सामान की तालाशी या अध्ययन प्रक्रिया के दौरान आप असहयोग व्यवहार करेंगे तो आपको बिना पैसे दिए अध्ययन से बाहर निकाल दिया जाएगा।

स्वयंसेवक के हस्ताक्षर _____

अध्ययन का संक्षिप्त विवरण

नमूने लेने की समय सूची	:	टैस्ट (A अथवा B): प्रत्येक अवधि में क्रमानुसार खुराक देने से पहले (दो बार) तथा दवा की खुराक देने के 0.250, 0.500, 0.750, 1.000, 1.500, 2.000, 2.500, 3.000, 3.500, 4.000, 5.000, 6.000, 7.000, 8.000, 10.000, 12.000, 16.000, 24.000, 30.000 तथा 36.000 घंटे बाद। रैफरैन्स (R): प्रत्येक अवधि में क्रमानुसार खुराक देने से पहले (दो बार) तथा दवा की सुबह की खुराक देने के 0.167, 0.250, 0.333, 0.500, 0.667, 0.833, 1.000, 1.333, 1.667, 2.000, 2.500, 3.000, 4.000, 6.000, 8.000, 10.000, 12.000, 12.167, 12.250, 12.333, 12.500, 12.667, 12.833, 13.000, 13.333, 13.667, 14.000, 14.500, 15.000, 16.000, 18.000, 20.000, 24.000, 30.000 तथा 36.000 घंटे बाद।			
रक्त संग्रह की मात्रा	:	कुल 78 बार नमूने लेना (जिनमें दवा की खुराक देने से पहले के दो बार लिये जाने वाले रक्त नमूने शामिल नहीं हैं), 4 मि० लि० प्रति नमूना। दवा की खुराक देने से पहले के दो बार लिये जाने वाले नमूनों के लिये 08 मि० ली०, चुनाव की जाँच के लिए 16 मि० ली०, व्यर्थ होने वाले 34.5 मि० ली० तथा अध्ययन के समाप्त होने पर होने वाले सुरक्षा विषलेषण के लिए 08 मि० लि० को शामिल करके प्रत्येक स्वयंसेवक से कुल 382.5 मि० ली० रक्त संग्रह किया जाएगा। टैस्ट (A अथवा B) के लिये: टैस्ट वर्ग (A अथवा B) में दवा की खुराक देने से पहले वाला रक्त नमूना लेने से लेकर दवा दिये जाने के पहले 24 घंटे बाद तक 89.0 मि० लि० रक्त संग्रह किया जाएगा। रैफरैन्स (R) के लिये: रैफरैन्स वर्ग (R) में दवा की खुराक देने से पहले वाला रक्त नमूना लेने से लेकर दवा दिये जाने के पहले 24 घंटे बाद तक 156.5 मि० लि० रक्त संग्रह किया जाएगा।			
छुट्टी होने के बाद यूनिट में आना	:	कोई नहीं।	भोजन की समय सूची	:	रात भर कम से कम 10 घंटे खाली पेट रहने के बाद आपको उच्चवसा युक्त तथा उच्चकैलोरी वाला नाश्ता दिया जायेगा तथा यह नाश्ता आपको 45 मिनट के अन्दर खाना होगा। प्रत्येक अवधि में सुबह की खुराक उच्चवसा युक्त तथा उच्चकैलोरी वाला नाश्ता शुरू करने के 45 मिनट बाद दी जायेगी। रैफरैन्स प्रोडक्ट की शाम की खुराक उच्चवसा

				युक्त तथा उच्चकैलोरी वाला रात का भोजन करने के 45 मिनट बाद दी जायेगी। आपको दोपहर का भोजन, जलपान, रात का भोजन, नाश्ता, दोपहर का भोजन और जलपान दवा की सुबह की खुराक देने के 4, 9, 11.25, 24, 28 तथा 33 घंटे बाद क्रमानुसार दिया जाएगा।	
वॉश आउट अन्तराल	:	कम से कम 05 दिन।	यूनिट में रहना	:	खुराक देने से कम से कम 11 घंटे पहले से लेकर खुराक देने के 36 घंटे बाद तक।
प्रतिबन्ध	:	आपको नाश्ता शुरू करने से पहले रात भर कम से कम 10 घंटे खाली पेट रहना होगा। प्रत्येक अवधि में दवा की खुराक सामान्य ताप पर 240 मि0 लि0 पीने के पानी के साथ उच्चवसा युक्त तथा उच्चकैलोरी वाला नाश्ता शुरू करने के 45 मिनट बाद दी जायेगी। रैफरैन्स प्रोडक्ट की शाम की खुराक उच्चवसा युक्त तथा उच्चकैलोरी वाला रात का भोजन करने के 45 मिनट बाद दी जायेगी। खुराक दिये जाने के 1 घंटे पहले से लेकर खुराक खाने के 2 घंटे बाद तक आपको पीने के लिए पानी लेने की आज्ञा नहीं होगी, खुराक देने के समय दिये जाने वाले 240 मि0 लि0 पीने के पानी को छोड़ कर (रैफरैन्स प्रोडक्ट की शाम की खुराक के लिये भी)। अध्ययन दवा लेने के 2 घंटे बाद तक आपको सीधे बैठे रहना है या फिर आप इधर-उधर घूम सकते हैं। इसके बाद आप सामान्य गतिविधियाँ, जिनमें अधिक शारीरिक परिश्रम शामिल न हो, कर सकते हैं। अगर आपकी तबियत खराब हो रही है तब आपको समुचित अवस्था में बैठाया जाएगा या फिर सीधी तरफ से लेटने की इजाजत दी जायेगी।			
क्लीनिकल सुरक्षा माप	:	अध्ययन की प्रत्येक अवधि में यूनिट में दाखिल होने के बाद, अध्ययन दवा की सुबह की खुराक देने से पहले तथा दवा की सुबह की खुराक देने के 2, 10, 14, 22 तथा 36 घंटे बाद मुँह के तापमान, बैठे रहने की स्थिति में रक्त दबाव तथा हाथ की नब्ज के जीव सम्बन्धी लक्षण तथा दुष्प्रभाव नापे/नोट किये जायेंगे। अध्ययन की प्रत्येक अवधि में जीव सम्बन्धी लक्षण निर्धारित समय के ± 2.0 घंटे की अवधि के अन्दर नापे जायेंगे। अध्ययन की प्रत्येक अवधि में स्वयंसेवको की संक्षिप्त क्लीनिकल जांच यूनिट में दाखिल होने पर तथा यूनिट से छुट्टी हाने पर करी जाएगी। अगर आपने अध्ययन दवा की खुराक का सेवन किया है तो अध्ययन के समाप्त होने पर लेबोरेट्री जाँचें जैसे हीमोग्लोबिन (Hemoglobin, रक्त रन्जक), रक्त के श्वेत कणों (white blood cells, वाइट ब्लड सैल) की कुल गणना, बिम्बाणु कणों (platelet, प्लेटलेट) की गणना, न्यूट्रोफिल कण (Neutrophils), लिम्फोसाइट कण (Lymphocytes),			

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	<p>मोनोसाइट कण (Monocytes), ईओसिनोफिल कण (Eosinophils), बेसोफिल कण (Basophils), कुल बिलिरुबिन (Total Bilirubin), सीरम क्रिएटीनिन (serum creatinine), ब्लड यूरीया नाइट्रोजन (blood urea nitrogen), सीरम एसपार्टेट अमाइनोट्रान्सफरेज (serum aspartate aminotransferase/AST), सीरम एलानिन अमाइनोट्रान्सफरेज (serum alanine aminotransferase/ALT), सीरम एल्कालाइन फॉस्फेटेज (serum alkaline phosphatase), रक्त में ग्लूकोज (blood glucose - fasting/random; खाली पेट रहने की अवस्था में/किसी भी अवस्था में) तथा सीरम कोलेस्टेरॉल (serum cholesterol) दोहराई जायेंगी।</p> <p>यदि ऊपर बतायी गई किसी भी लेबोरेट्री जाँच का परिणाम लेबोरेट्री जाँचों की स्वीकार्य सीमाओं (acceptable limits) से बाहर पाया जाता है, तो इन लेबोरेट्री जाँचों के परिणामों के सामान्य होने/क्लीनिकल रूप से महत्वपूर्ण न होने तक आपको फॉलो अप (follow-up) के लिए आना होगा।</p>
इलाज	<p>: रैफरैन्स (R):</p> <p>क्योवा हक्को कोगियो कम्पनी लिमिटेड, जापान (Kyowa Hakko Kogyo Co. Ltd., Japan) की एलीलौक 5 मि0 ग्रा0 गोली (ALLELOCK® 5 mg tablet)।</p> <p>टैस्ट (A अथवा B):</p> <p>रैनबैक्सी लेबोरेट्रीज लिमिटेड, भारत की ओलोपैटाडीन हाइड्रोक्लोराइड 10 मि0 ग्रा0 दीर्घ निस्तार होने वाली गोली (olopatadine hydrochloride 10 mg extended release tablet)।</p>
खुराक	<p>: ओलोपैटाडीन हाइड्रोक्लोराइड 10 मि0 ग्रा0 दीर्घ निस्तार होने वाली गोली (olopatadine hydrochloride 10 mg extended release tablet) की मुख द्वारा दी गई एक खुराक को उच्चवसा युक्त तथा उच्चकैलोरी वाला नाश्ता शुरू करने के 45 मिनट बाद दिया जाएगा।</p> <p>अध्ययन की प्रत्येक अवधि में एलीलौक 5 मि0 ग्रा0 गोलियों (ALLELOCK® 5 mg tablets) की मुख द्वारा दी गई दो खुराकों (प्रत्येक खुराक में ओलोपैटाडीन हाइड्रोक्लोराइड 5 मि0 ग्रा0 है, जिन्हें 12 घंटे के अन्तराल पर दिया जायेगा; कुल खुराक 10 मि0 ग्रा0) दी जायेगी। सुबह की खुराक उच्चवसा युक्त तथा उच्चकैलोरी वाला नाश्ता शुरू करने के 45 मिनट बाद दी जायेगी। अध्ययन की प्रत्येक अवधि में शाम की खुराक उच्चवसा युक्त तथा उच्चकैलोरी वाला रात का भोजन करने के 45 मिनट बाद दी जायेगी।</p>

घोषणा

मैं यह घोषणा करता हूँ कि :-

- इस अध्ययन में भाग लेना मेरी अपनी इच्छानुसार है।
- यह अध्ययन एक अनुसंधान परियोजना है तथा इस अध्ययन से मुझे कोई चिकित्सा लाभ नहीं होगा।
- अध्ययन अवधि के दौरान उठने वाले प्रश्नों का उत्तर लेना मेरा अधिकार है।
- मुझे यह बता दिया गया है कि यदि अध्ययन के दौरान किसी नई महत्वपूर्ण जानकारी का ज्ञान होता है, तो मुझे उससे अवगत कराया जाएगा।
- मैं किसी भी समय अध्ययन से अपना नाम वापस ले सकता हूँ। भविष्य में मिलने वाली चिकित्सा सुविधा व भावी अध्ययनों के लिए होने वाले चयन का इससे कोई सरोकार नहीं है।
- मुझे अपने स्वास्थ्य की रक्षा अथवा अध्ययन के करार (प्रोटोकाल) के उल्लंघन करने पर किसी भी समय अध्ययन से हटाया जा सकता है।
- मैंने सूचित सहमति पत्र को पढ़ और समझ लिया है तथा अध्ययन आदिलेख (प्रोटोकाल) का पालन करने में मुझे कोई परेशानी नहीं है।
- रैनबैक्सी लेबोरेट्रीज लिमिटेड की स्वयंसेवक भर्ती करने से सम्बन्धित मेरी निर्देश/सन्दर्भ संख्या आर0 एल0 एल0/एम0 ए0 जे0/RLL_MAJ_____ है।
- मुझे इस समय किसी भी चिकित्सीय इलाज या सुविधा की जरूरत नहीं है।
- मैंने अपने पूर्व चिकित्सा इतिहास तथा वर्तमान में किसी भी दवा के सेवन के सम्बन्ध में कोई सूचना नहीं छुपाई है।
- मैंने सहमति पत्र को ध्यानपूर्वक पढ़ लिया है तथा अध्ययन, संभावित दुष्प्रभाव अथवा सहमति पत्र के बारे में सभी प्रश्नों का मुझे संतोषप्रद उत्तर मिल गया है।
- मेरी व्यक्तिगत जानकारी तथा मुझसे सम्बन्धित कोई भी जानकारी, जो मैंने स्वयंसेवक का नाम दर्ज करने के फार्म में प्रदान करी है अथवा चुनाव की जाँच के दौरान या अध्ययन प्रक्रियाओं के दौरान प्राप्त होने वाली जानकारी (जिसमें पहचान संख्या अथवा मेरे दैहिक, फिजियोलौजिकल, मानसिक, आर्थिक, सांस्कृतिक अथवा सामाजिक व्यक्तित्व से सम्बन्धित विशिष्ट घटक शामिल हैं) को अध्ययन की आवश्यकताओं के अनुसार प्रोसेस करने के लिये मैं अपनी स्वैच्छिक सहमति देता हूँ। जानकारी को प्रोसेस करने के लिये भी मैं अपनी स्वैच्छिक सहमति देता हूँ।
- मुझे इस बात की जानकारी है की अध्ययन प्रक्रियाओं की आवश्यकताओं के अनुसार मेरे जैविक नमूनों को नाम रहित किया जायेगा अथवा नष्ट किया जायेगा।

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APPROVED

BY

Jamia Hamdard Institutional Review Board

Hamdard Nagar, New Delhi

- यथोचित अन्तराल पर तथा अधिक देरी के बिना, यह जानकारी लेना कि मुझसे सम्बन्धित जानकारी प्रोसैस हो रही है या नहीं, मेरा अधिकार है।
- यह मेरा अधिकार है, जब तक कि कानून द्वारा अथवा किसी अनुबन्ध का निर्वाह करने के दौरान वर्जित न हो, मैं यथोचित तरीकों से अपने जायज़ हितों का बचाव करूँ।
"मेरी व्यक्तिगत जानकारी पर कोई भी ऐसी स्वाचालित क्रिया नहीं करी जायेगी जिससे मैं किसी स्वाचालित निर्णय के अधीन आता हूँ अथवा जो मुझ पर कानूनी प्रभाव डालती है अथवा मुझे महत्वपूर्ण रूप से प्रभावित करती है।"
"मेरी व्यक्तिगत जानकारी पर कोई भी ऐसी स्वाचालित क्रिया नहीं करी जायेगी जिससे मेरे कुछ निजी पहलूओं का मूल्यांकन होता है, जैसे काम करने की क्षमता/निष्पादन, उधार लेने की योग्यता, विश्वसनीयता, चाल चलन/आचरण इत्यादि।"
- मैं प्रमाणित करता हूँ कि पिछले 90 दिनों के दौरान मैंने यहाँ अथवा ओर कहीं किसी भी प्रायोगिक अध्ययन में भाग नहीं लिया है।
- मैं जामिया हमदर्द परिसर में रहने के दौरान अनुशासन का पालन करूँगा।
- अगर इस अनुसंधान अध्ययन के सम्बन्ध में अन्य कोई जानकारी अथवा अनुसंधान सम्बन्धी कोई आघात या चोट लगने पर मैं जॉचकर्ता (011-2995-6721) अथवा डा० तोसिफ मोनिफ, अध्ययन निर्देशक (91-124- 4231001) से सम्पर्क कर सकता हूँ। स्वयंसेवक के रूप में अपने अधिकारों की जानकारी के लिए मैं डा० फरहान जालीस एहमद, संयोजक/सदस्य सचिव, जामिया हमदर्द इन्सटीच्युशनल रीवीयु बोर्ड (टेलीफोन नम्बर 9810720387) से सम्पर्क कर सकता हूँ।
- मेरे हस्ताक्षर यह प्रमाणित करते हैं कि यह सहमति जानकारी के आधार पर दी है, तथा मैंने बिना पूर्वाग्रह भाग लेना स्वीकार किया है।

स्वयंसेवक के हस्ताक्षर तथा तारीख/अंगूठे का निशान*	:	
निष्पक्ष गवाह के हस्ताक्षर तथा तारीख*	:	
निष्पक्ष गवाह का नाम तथा स्वयंसेवक के साथ उसका सम्बन्ध	:	

स्वयंसेवक के हस्ताक्षर _____

मैं यह घोषणा करता हूँ कि रैनबैक्सी से मेरा कोई सम्बन्ध नहीं है।		
सूचित सहमति लेने वाले व्यक्ति के हस्ताक्षर तथा तारीख	:	
जॉचकर्ता के हस्ताक्षर तथा तारीख	:	

* अनपढ़ स्वयंसेवक के लिये।

घोषणा: इस सूचित सहमति पत्र (पत्र A तथा पत्र B) की हस्ताक्षर करी हुई एक कोपी/प्रतिलिपि मुझे प्रदान कर दी गई है।
स्वयंसेवक के हस्ताक्षर तथा तिथि _____

APPENDIX III.
ANNEXURE III

INFORMED CONSENT FORM -A

**GENERAL INFORMATION OF A BIOAVAILABILITY/BIOEQUIVALENCE
STUDY IN HEALTHY, ADULT, HUMAN SUBJECTS CONDUCTED AT
CLINICAL PHARMACOLOGY UNIT, RANBAXY LABS LTD.**

Dear Volunteer,

This document has been prepared to provide information required for your participation in a bioavailability/bioequivalence study. Please read this information and clarify if you have any queries before you decide to participate in the study.

- This is a research based study. You are being asked to participate in this research study.
- Take all the time you need to read and understand the information, before agreeing to participate in this study.
- If you are not able to understand any part of this document, please feel free to get your doubts clarified. An oral presentation of this document will also be held in the language you understand.
- Please sign the informed consent forms (A and B) and submit it for our records. You will be provided a copy of the same for your reference and record.
- During your participation in the clinical study, you will act as an independent individual, and not as an agent, partner or an employee of Ranbaxy Laboratories Limited.

PURPOSE OF THE STUDY

Bioavailability is the amount of a drug that becomes available in the body (eg: blood, urine) after consuming the drug. Two drugs are said to be bioequivalent if the amount of drug in the body (eg: blood, urine) are similar after consuming the drugs.

Signature of Volunteer_____

ANNEXURE III

Bioequivalence has to be proven between the marketed drug named reference and the generic drug (to be marketed) named test. Government agencies check the details of the results from the bioequivalence studies. When they are convinced that the two drugs are similar (bioequivalent), the test drug may be approved for marketing

GENERAL PROCEDURE OF A BIOAVAILABILITY/BIOEQUIVALENCE STUDY

Given below is a general explanation of how a bioavailability/bioequivalence study is conducted.

You will be admitted to the study if you pass the screening tests and provide a written informed consent. On day of admission, breath test for alcohol, drug of abuse in urine and or other tests if required by the protocol will be done in each period. Baggage and pocket(s) will be checked prior to admission and you are not allowed to carry alcohol, xanthine, tobacco, cigarette, illicit drug, medicine in any form, any eatables (solid and liquid) and any electrical or battery operated appliances other than wrist watch and mobile phone without camera. You will be provided with Ranbaxy volunteer uniform(s) during your in-house stay. During your participation in this study, you will be provided lockers to keep your belongings and an identity card which will be required to be displayed during in-house stay. You may be monitored (e.g. through Close Circuit TV-camera) during your stay at CPU.

During the stay in the unit you will be provided standardized meal. (For detailed meal plan refer to study summary in INFORMED CONSENT FORM - B).

You will be required to consume one of the study drugs (either the test or reference) in each period.

As per protocol, blood samples will be collected at pre-determined time intervals in vacutainers (tubes) through a disposable needle and cannula which will be inserted into a blood vessel and kept fixed at the site. To prevent the needle from getting blocked, solution of heparin (which is a normal body constituent) will be added. Half milliliter of heparinised blood will be discarded before sample collection. Alternatively, blood

Signature of Volunteer_____

ANNEXURE III

samples may also be collected, directly with a sterile disposable needle and syringe. The collected samples will be processed and stored appropriately for further analysis. (Please refer to INFORMED CONSENT FORM - B for Sample collection time points.)

As per the study requirement other biological specimen (e.g.: Urine, Stool, Sputum samples etc) may be collected at predetermined time intervals.

Pain, swelling and/or numbness of the arm may occasionally result from the blood collections during the study. This procedure may also occasionally cause light headedness or fainting. These reactions are usually of short duration and are reversible.

After the completion of in-house stay, you will be discharged, with information to return on a specific date at a specific time for the subsequent period(s) of the study or for walk-in samples (ambulatory samples or for end of study safety sample), vital signs measurement and adverse event monitoring, if required.

Similar procedures will be followed in the subsequent period(s) except for the informed consent procedure.

RESTRICTIONS TO BE FOLLOWED

If you participate in this study as a subject, you will be required to follow certain restrictions:

You will not be allowed to have tea, coffee, chocolates and cola during your stay in the unit. For 48 hours prior to admission and during the course of the study till last sample collection for pharmacokinetic analysis, you must not consume any alcohol or any products that contain alcohol (beverages, marinades, medicines, etc), grapefruit juice and / or grapefruit supplements. You must not have taken any medication including over the counter (OTC) medications 30 days before and throughout the study. Drinking water will be restricted before and after consuming the drug. Posture restriction will also be enforced after dosing. (For specific details of restrictions related to drinking water and posture, refer ICF - B).

Signature of Volunteer_____

ANNEXURE III

BENEFITS

Since you do not require treatment with the study drug(s), you will receive no medical benefit from this study, other than the benefit of a free health check-up and the satisfaction of serving the interests of human beings in poor health.

NEW FINDINGS

Any new and important information which may be discovered during the study which may influence your willingness to continue in the study will be made available to you as soon as possible.

ALTERNATIVE TREATMENT

Since this study is for research only and the alternative would be not to participate.

INSURANCE POLICY

You are insured under the insurance policy no. OG-11-1113-3306-00000009 of Bajaj Allianz and you will be compensated in case of a trial related injury.

MAINTENANCE OF DISCIPLINE

You are expected to follow certain rules of the CPU and maintain discipline during your stay in the unit. In case you do not behave properly in the CPU you will be withdrawn from the study without any payment and/or excluded from participating in all future studies.

Signature of Volunteer_____

ANNEXURE III

DETERMINATION OF FINANCIAL COMPENSATION DUE IN CASES NOT COMPLETING THE STUDY

1	Withdrawn from the study by the Investigator on objective medical grounds to safeguard your health, before administration of study drug	On pro-rata basis
2	Withdrawn from the study by the Investigator on objective medical grounds to safeguard your health, after administration of study drug	Full payment on completion of study/ follow-up visits
3	Dropped-out of the study, on your own accord, after administration of study drug	On pro-rata basis
4	Dropped from the study on compassionate grounds, with the permission of Investigator	On pro-rata basis
5	Withdrawn from the study by the Investigator due to your failure to comply with the requirements of the study	On pro-rata basis
6	Withdrawn from the study by the Investigator because of your wilful withholding of information regarding your past or present medical illness(es) relevant to the study and your misbehaviour during the study	No payment
7	Non-compliance with the prescribed time-schedule for the follow-up visit (where applicable)	50% of the payment due for that visit

CONFIDENTIALITY

Records of your participation in this study will be confidential so far as permitted by law. However, the confidential data which identifies you by name will be available to the study personnel, Corporate Quality Assurance Auditor during audits and to the

Signature of Volunteer_____

ANNEXURE III

Institutional Review Board (IRB) & various regulatory agencies, as it becomes necessary. Any publication of the data will not identify you by name. Investigator's representatives/ designates shall act as data custodian for this study till it is sent for archiving.

MEDICAL TREATMENT FOR INJURY

In case of study related side effect(s), medical care will be offered at the Clinical Pharmacology Unit and treatment of side effect or event requiring hospitalization will be carried out at a nearby hospital and the expenses will be borne by Ranbaxy Laboratories Limited

VOLUNTARY NATURE OF PARTICIPATION

Your participation in this study is entirely your choice. Whether you choose to participate or not will not involve any penalty or affect your selection for any future studies. You may also stop participating in the research at any time you wish. It is your choice and all your rights will be respected.

Note: The Investigator can stop your participation in the study if the following are known- it appears to be harmful to your health; you fail to fulfill study requirements; you have withheld information related to your health record; the study is cancelled.

In case of emergency you can also call the study personnel by pressing the emergency bell which is available in the ward and toilet areas.

CONTACT DETAILS

At any time before, during or after the study, you can obtain further information about this study. In case of medical emergencies during the study, or if you have any urgent questions or queries concerning discomfort or injury associated with the study, please contact, Investigator at Ranbaxy Clinical Pharmacology Unit, Majeedia Hospital 2nd Floor, Hamdard Nagar, New Delhi 110 062, Telephone: 2995-6721.

Signature of Volunteer_____

ANNEXURE III

If you have questions regarding your rights as a research subject, you may call Dr. Farhan Jalees Ahmad, Convener/Member Secretary, Jamia Hamdard Institutional Review Board (Telephone number 9810720387).

Note: You may also consult your family doctor at any time during the study

Signature of Volunteer_____

ANNEXURE III

INFORMED CONSENT FORM- B (STUDY INFORMATION)

Single dose three-way crossover bioavailability study on Amoxicillin extended release tablets 775 mg in healthy adult human subjects under fed condition

Version No. : 01

Supersedes : Not Applicable

This document provides information regarding this bioavailability study. Please read this information and clarify if you have any queries before you decide to participate in this study. If you agree to participate please sign the document and submit for our records.

This study involves research to evaluate the amount of drug in the blood after administration of extended release tablet formulation containing Amoxicillin 775 mg.

INTRODUCTION

Amoxicillin is a semi-synthetic antibiotic, an analog of ampicillin, with bactericidal activity against gram-positive and gram-negative microorganisms. Amoxicillin exerts its bactericidal action against susceptible organisms during the stage of multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide. Amoxicillin is a penicillin-class antibacterial indicated for the treatment of tonsillitis and/or pharyngitis secondary to Streptococcus pyogenes (S. pyogenes) in adults and pediatric patients 12 yrs and older.

In this three period study two batches of Amoxicillin extended release tablets 775 mg of Ranbaxy Laboratories Limited, India will be compared with MOXATAGTM (Amoxicillin extended release tablets) 775 mg of MiddleBrook Pharmaceuticals, Inc., Germantown, Maryland 20876 USA in 15 healthy, adult, human subjects under fed condition.

Dosage

The recommended dose of amoxicillin extended release tablets is 775 mg once daily taken within 1 hour of finishing a meal for 10 days. The full 10-day course of therapy

Signature of Volunteer_____

ANNEXURE III

should be completed for effective treatment of tonsillitis and/or pharyngitis secondary to *S. pyogenes*.

ADVERSE EVENTS

The most frequently reported adverse reactions ($\geq 1\%$) which were suspected or probably related to amoxicillin extended release tablets in patients are diarrhea, nausea, vomiting, abdominal pain and headache.

In a single and multiple dose pharmacokinetics study conducted on 20 healthy male and female subjects with amoxicillin extended release tablet 775 mg, the most common adverse event was headache, reported by 6 (30%) of subjects. The majority of adverse events were mild in severity. There were no clinically significant laboratory abnormalities.

In a Phase I bioequivalence study conducted on 26 healthy male and female subjects with single dose of amoxicillin extended release tablet 775 mg, the adverse events reported were pain, diarrhea, nausea, headache and dizziness.

Note:

You can participate in this study if you:

- Have hemoglobin level ≥ 13.0 g/dL (for males) and ≥ 12.0 g/dL (for females).

You cannot participate in this study if you

- Have history of hypersensitivity to Amoxicillin or related group of drugs.
- Have history of recurrent headache.
- Have history of nausea, vomiting, abdominal pain and/or diarrhea in the week preceding the study.
- Have history of drug-induced rash and/or pruritis.

Note: (For female volunteer only):

You can participate in this study if you are

Signature of Volunteer_____

ANNEXURE III

- Of childbearing potential, is practicing or willing to practice an acceptable method of birth control for the duration of the study as judged by the investigator(s), such as condoms, foams, jellies, diaphragm, intrauterine device (IUD), or abstinence; or
- Are postmenopausal for at least 1 year; or
- Are surgically sterile (bilateral tubal ligation, bilateral oophorectomy / hysterectomy).

You cannot participate in this study if you are

- Demonstrating a positive urine pregnancy test prior to admission of period I.
- Currently breast-feeding mother.

Caution:

- Avoid operating machines or driving vehicles during the entire conduct of the study.
- If you feel unwell or experience any uneasiness, please bring to the notice of the Medical Officer/Nurse/staff on duty immediately.
- Female volunteers are advised to use acceptable method of birth control for the duration of the study, such as condoms, foams, jellies, diaphragm, intrauterine device (IUD), or abstinence.

NUMBER OF SUBJECTS: Fifteen (15)

INSURANCE POLICY

You are insured under the insurance policy no. OG-11-1113-3306-00000009 of Bajaj Allianz and you will be compensated in case of a trial related injury.

CONTACT DETAILS

At any time before, during or after the study, you can obtain further information about this study. In case of medical emergencies during the study, or if you have any urgent questions or queries concerning discomfort or injury associated with the study, please contact Principal Investigator/medical officer at Clinical Pharmacology Unit, Ranbaxy

Signature of Volunteer_____

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Laboratories Limited, Majeedia Hospital 2nd Floor, Hamdard Nagar, Delhi, India.
Telephone no.: (011-2995-6721) (office).

If you have questions regarding your rights as a research subject, you may call Dr. Farhan Jalees Ahmad, Convener/Member Secretary, Jamia Hamdard Institutional Review Board (JHIRB), Telephone number 9810720387

Note: You may also consult your family doctor at any time during the study.

FINANCIAL COMPENSATION

You shall be adequately compensated on account of your participation in the study as per the guidelines issued by the JHIRB. The compensation in this study will be Rs. 4500/- (Rupees four thousand five hundred) per subject, which will be paid proportionately for participation at the end of each period of the study. This is to compensate you for your discomfort and inconvenience. From the period I payment, a sum of Rs. 500/- will be deducted and given to you after satisfactory resolution of the end of the study safety assessment.

In addition, as a token of appreciation- a sum of Rs 1800/- (Rupees one thousand eight hundred only) will be paid to only those subjects who complete the study successfully or are withdrawn from the study by the Investigator for reasons other than protocol violation by the subject.

Signature of Volunteer_____

ANNEXURE III

STUDY SCHEDULE

Sampling schedule	:	Each blood sample of 4 ml Predose (duplicate) and at 0.500, 1.000, 1.333, 1.667, 2.000, 2.250, 2.500, 2.750, 3.000, 3.250, 3.500, 3.750, 4.000, 4.333, 4.667, 5.000, 5.500, 6.000, 8.000, 10.000, 12.000, 16.000, 20.000 and 24.000 hours post-dose in each period.			
Total blood volume	:	Total of 372 ml (Note: extra blood sample may be collected if required for safety). The volume of blood collected from pre-dose blood sample till first 24 hours post-dose in each period shall be 116 mL.	Ambulatory Visit	:	None
Housing	:	Approximately 11 hours prior to dose until 24 hours post-dose.	Washout Period	:	At least seven (07) days
Meal schedule	:	You will be served dinner on admission night at approximately -10.5 hours of dosing. You will be served high-fat breakfast [consisting of White Bread 84 gms with butter 10 gms, Paneer Bhurji (Paneer 100 gms, Onion 20 gms, Tomato 20 gms and Oil 5 gms), Salted Peanut 15 gms and 200 mL of whole milk with 5 gms of sugar; Total 930 K calories] 45 minutes before dosing in each period. Lunch, snacks and dinner will be provided at 4, 9 and 13 hours post dose respectively.	Restrictions	:	You shall be required to fast at least 10 hr before starting the high-fat breakfast. You will be dosed while seated and will be remain seated or ambulatory for the first 2 hours following each drug administration. Drinking water will not be allowed from 1 hour before dosing until 2 hours post dose except 240 ml of water given during administration of the dose. Thereafter, drinking water will be allowed at all times.
Clinical Safety Measurements	:	Vital signs – Vital signs (oral temperature, sitting BP and radial pulse) measurement will be performed after admission, prior to dosing (within 2.0 hours) and at 2, 6 and 24 hours post dose (within ±2.0 hours) in each period. Adverse event monitoring will be done after admission, prior to dosing and at approximately 2, 6, and 24 hours post dose in each period. Brief Clinical examination: will be done after admission and before discharge in each period. Laboratory parameters of biochemistry and hematology will be repeated at the end of the study at 24 hours post dose of Period III in case you have been administered study drug. Additionally, urine pregnancy test (for female volunteers only) will be carried out at this time point. However, in case the subject does not report at the scheduled visit or if it is deemed necessary to delay the assessment of lab parameters for medical reasons, the laboratory parameters will be repeated at any subsequent visit. In case laboratory			

Signature of Volunteer_____

ANNEXURE III

		parameter(s) is (are) outside the acceptable limits, you will have to come for follow up until the results are normal / clinically not significant.
Treatments	:	Reference (R): MOXATAG™ (Amoxicillin extended release tablets) 775 mg of MiddleBrook Pharmaceuticals, Inc., Germantown, Maryland 20876 USA. Test (A and B): Amoxicillin extended release tablets 775 mg of Ranbaxy Laboratories Limited, India.
Dose	:	Either of test (A or B) or reference (R) products containing Amoxicillin extended release tablets 775 mg will be administered with 240 mL of drinking water, 45 minutes after the start of a high fat breakfast, at an ambient temperature under supervision of trained study personnel in each period.

DECLARATION

I hereby declare that:

- My participation in this study is voluntary.
- This study is a research project and provides me no medical benefits.
- I have the right to be provided with answers to questions arising during the course of the study.
- I will be provided any significant new findings coming to light during the research investigation.
- I can withdraw from the study at any time without prejudice to future medical care or selection for future studies.
- I can be withdrawn from the study at any time if I violate the study protocols or to protect my health.
- I have read and understood the Informed consent form and have no problem(s) in complying with the study protocol.
- My reference number with respect to volunteer enrolment of Ranbaxy Laboratories Ltd. is RLL_MAJ_____
- I currently require no medical treatment or care.
- I have withheld no information regarding my past medical history and current drug intake.

Signature of Volunteer_____

ANNEXURE III

- I have read the consent form and any questions I had about the study, possible side effects or the consent form, have been answered to my satisfaction.
- I voluntarily give my consent for my personal data related to any information relating to me, as I have provided in the enrollment form, or as it is generated during screening and study procedures, including identification number, or factors specific to my physical, physiological, mental, economic, cultural or social identity, to be processed as required for the study requirements. I also voluntarily give my consent for the processing of data.
- I am aware that my biological samples shall be anonymized or destroyed as per the requirements of the procedures of the study.
- It is my right to obtain information at reasonable intervals and without excessive delay regarding whether or not data relating to me are being processed.
- It is my right that, unless required by law, or while fulfilling a contract, with suitable measures to safeguard my legitimate interests: “No automated processing of my personal data shall be done which makes me subject to a automated decision, produces legal effects concerning me or significantly affects me.”
- “No automated processing of my personal data shall be done to evaluate certain personal aspects relating to me, such as my performance at work, creditworthiness, reliability, conduct, etc.”
- During the past 90 days I have not participated in any experimental studies conducted here or elsewhere.
- I will maintain discipline during my stay at the Jamia Hamdard campus.
- If I have any further questions regarding this research study or in the event of research related injury, I may contact Investigator (011-2995-6721) or Dr. Tausif Monif, Study Director (91-124- 4231001). I may contact Dr. Farhan Jalees Ahmad, Convener/Member Secretary, Jamia Hamdard Institutional Review Board (Telephone number 9810720387), if I have any questions regarding my rights as a volunteer.
- My signature confirms that consent is based on information provided and that I had freely chosen to participate without prejudice.

Signature of Volunteer_____

Annexure III

**Volunteer's Signature & Date/ Thumb
impression***

:

Impartial witness's Signature & Date*

:

**Impartial witness's Name and his/her
relation with Volunteer**

:

**I hereby declare that I have no relation
with Ranbaxy**

:

**Signature of Person Obtaining Consent &
Date**

:

Investigator's Signature & Date

:

* In case of illiterate volunteer

Declaration: I have received the signed copy of this ICF (FORM A and FORM B)

Volunteer's signature & Date



CONSENT TO PARTICIPATE IN RESEARCH

Title of Research: Socio-ethico-legal dilemmas of 'informed consent' as applicable to human subject research in India

Introduction and Purpose

My name is Himani Bhakuni, I am a PhD student at the University of Edinburgh, United Kingdom, working with my faculty advisor, Professor Anne Griffiths, in the School of Law. I would like to invite you to take part in my research study, which concerns understanding the dynamics and the process through which the legal and ethical right of informed consent is realised within the paradigm of biomedical research in India. The principal research questions ask how the right to informed consent is operationalised within clinical trials in India. It seeks to understand how the bureaucrats, regulators, investigators and ethics committees responsible for bringing the principle of informed consent into practice view the principle in their respective roles and what the principle means to the trial participants and other stakeholders in clinical research. My lens is socio-legal; hence, the research looks at law's interactions with individuals and institutional actors. It is about understanding the 'practice' of informed consent within the Indian context.

Procedures

If you agree to participate in my research, I will conduct an interview with you at a time and location of your choice. The interview will involve questions about your experiences and views on ethical issues in clinical research. It should last about 30 minutes, but could be less or more depending on how much time you are willing to share. With your permission, I will audiotape and take notes during the interview. The recording is to accurately record the information you provide, and will be used for transcription purposes only. If you choose not to be audiotaped, I will take notes instead. If you agree to being audiotaped but feel uncomfortable at any time during the interview, I can turn off the recorder at your request. **If you do not wish to continue, you can stop the interview at any time.**

I expect to conduct only one interview; however, follow-ups may be needed for added clarification. If so, I will contact you by e-mail/phone to request this.

Benefits

There is no direct benefit to you from taking part in this study. It is hoped that the research will generate a better understanding of the concept of informed consent and what it means to the people involved in the process of giving and realising consent so that such an understanding may allow for better mechanisms for bringing it into being

Risks

There are no risks involved with participating in this study. Your confidentiality is of utmost importance and that will not be compromised in any manner. If there is any interview question that makes you uncomfortable, you are allowed to put the interview on hold or stop the interview altogether.

Confidentiality

Your study data will be handled as confidentially as possible. If results of this study are published or presented, individual names and other personally identifiable information will not be used unless you give explicit permission for this below.

To minimize the risks to confidentiality your data will be stored on password protected disk space on the personal laptop of the researcher and all the data will be coded and encrypted. There will be

limited access to my study records. **If you do not want to sign an informed consent form, I will take your consent orally and will hand you a copy of this form for your records.**

When the research is completed, I may save the tapes and notes for use in future research done by myself or others. I will retain these records for up to 10 years after the study is over. The same measures described above will be taken to protect confidentiality of this study data.

Compensation

You will not be paid in cash or kind for taking part in this study.

Rights

Participation in research is completely voluntary. You are free to decline to take part in the research. You can decline to answer any questions and are free to stop taking part in the research at any time. You have the right to request to withdraw the use of your data after the interview but only up to the time the results of the study are ready to be disseminated.

Questions

If you have any questions about this research, please feel free to contact me. I can be reached at Mobile: +91 9910771685 (India) +4407778292855 (UK) or at himani.bhakuni@ed.ac.uk

If you have any questions about your rights or treatment as a research participant in this study, please contact the University of Edinburgh, School of Law, Research and Ethics Integrity Committee (REIC) at law.ethicsreview@ed.ac.uk or Tel: +44 (0)131 650 2008

CONSENT

If you agree to participate, please say so or sign the form below. You will be given a copy of this consent form to keep for your own records.

If you wish to participate in this study, please sign and date below.

Participant's Name (*please print*)

Participant's Signature

Date

[Optional]

If you agree to allow your name or other identifying information to be included in all final reports, publications, and/or presentations resulting from this research, please sign and date below.

Participant's Signature

Date

Regarding an appointment with Dr.

BHAKUNI Himani

Thu 19/05/2016 05:34

Sent Items

To: s@nic.in < @nic.in>;

Dear Mr. ~~Singh~~_____

In pursuance to my call to you here is the email seeking an appointment with Dr. _____ on any day as per his schedule.

My name is Himani Bhakuni, I am a PhD student at the University of Edinburgh, United Kingdom, working with my faculty advisor, Professor Anne Griffiths, in the School of Law. My research concerns understanding the dynamics and the process through which the ethical and legal right of informed consent is realised within the paradigm of biomedical research in India. The principal research questions ask how the right to informed consent is operationalised within clinical trials in India and whether informed consent is a right without a remedy in that context. It seeks to understand how the various institutional actors, practitioners, researchers, bureaucrats, regulators, investigators, and ethics committees responsible for bringing the principle of informed consent into practice view the principle in their respective roles and what the principle means to other stakeholders in clinical research. My lens is socio-legal; hence, the research looks at law's interactions with individuals and institutional actors. It is about understanding the 'practice' of informed consent within the Indian context.

For this, I would like to speak with Dr. _____, as being _____ he would definitely realize the importance of research being done on this topic.

Confidentiality is a major aspect of this research, individual names and other personally identifiable information will not be used in my research unless the participants give explicit permission to do so.

I am currently in New Delhi for the purpose of this research. I can be reached at the email address: himani.bhakuni@ed.ac.uk or alternatively at my **mobile number: 9910771685.**

I am hoping you could get me an appointment to meet with _____ whenever he returns to New Delhi.

Thank you and looking forward to hearing from you.

Sincerely,

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<http://www.law.ed.ac.uk/research/students/viewstudent?ref=324>

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